Cardiorenal syndrome

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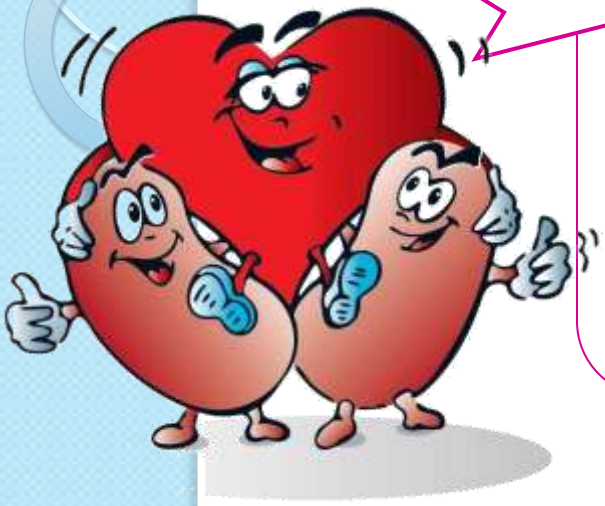
NMGH

DNG
Dakahlia Nephrology Group
رابطة أطباء الكلى بالدقهلية

Agenda

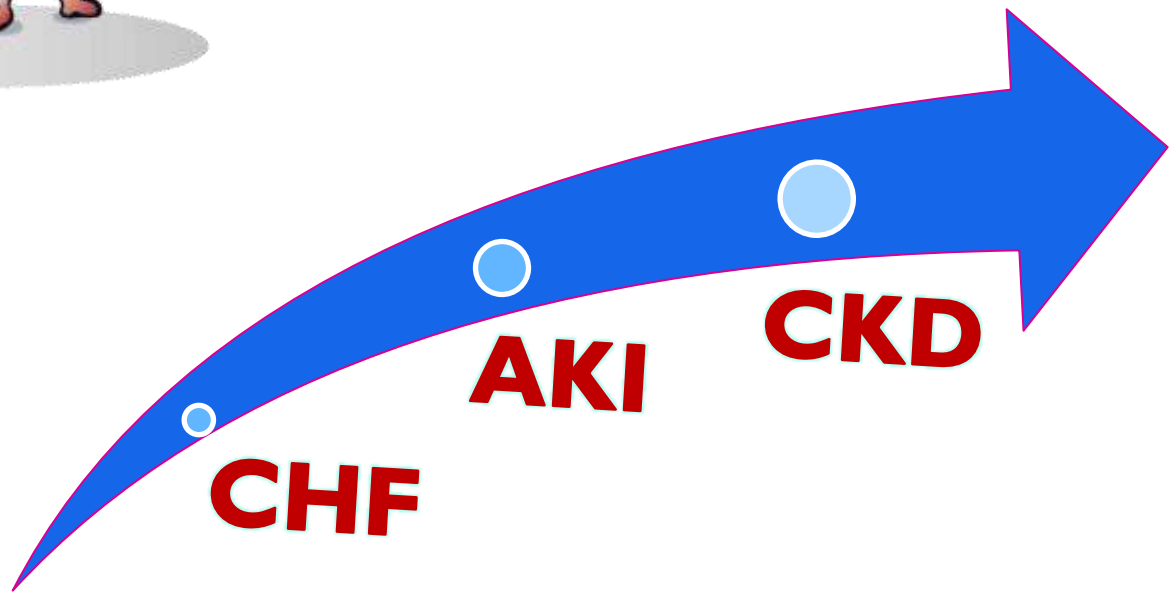
- Definition
- Classifications
- Pathophysiology
- Treatment

2004



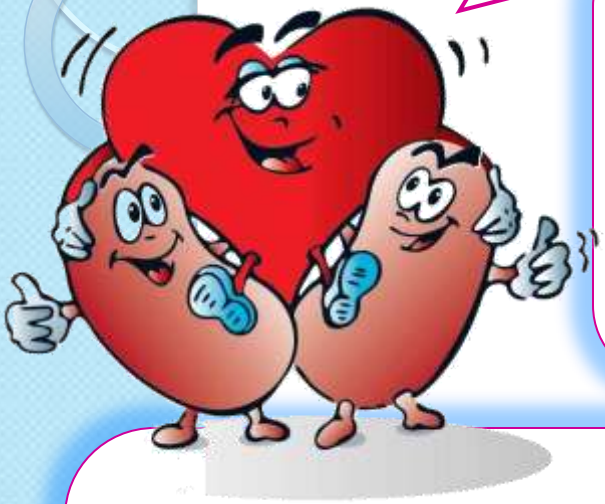
Cardio –renal syndrome

Acute and chronic renal responses are due to primary impairment of cardiac function(CHF).



Bongartz et al'. Eur Heart J 2005; 26: 11–17. Heywood, Heart Fail Rev 2004; 9: 195–201
Shlipak MG, Massie , Circulation 2004; 110: 1514–1517.

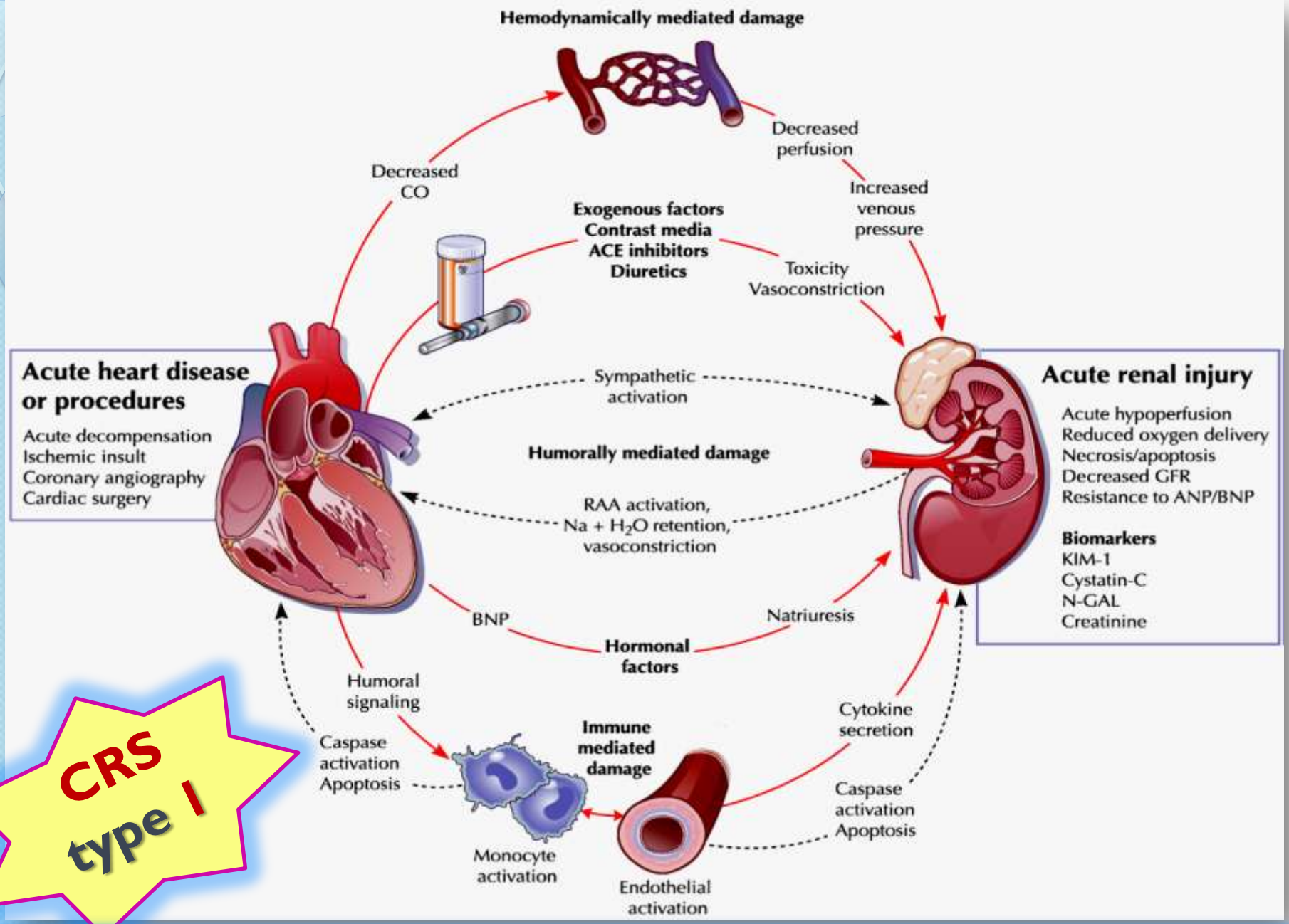
2010



(**stress the bi-directional nature of the heart-kidney interactions**).

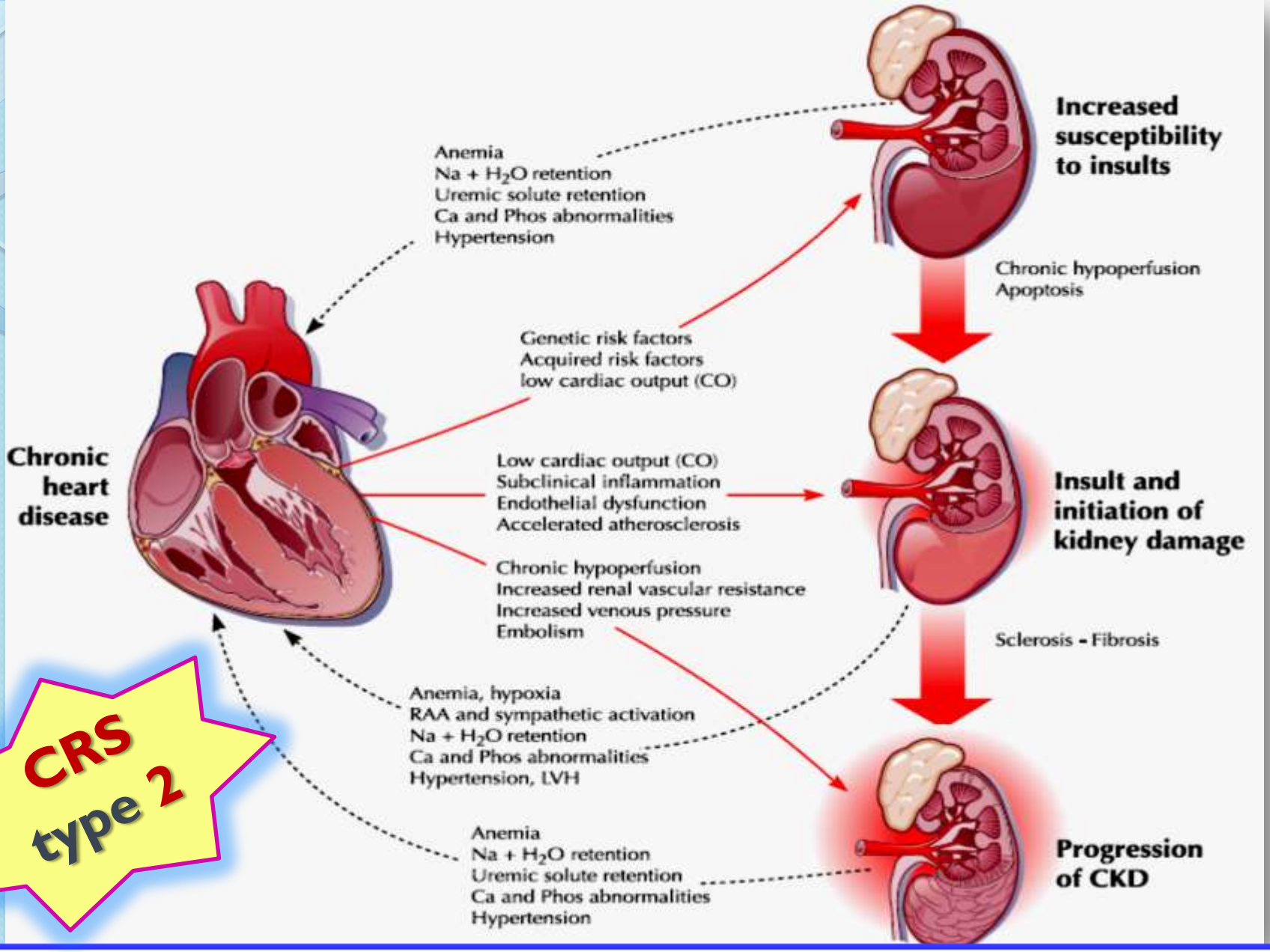
Term CRS was used to identify a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ

Ronco et al., **Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative.** Eur Heart J. 2010 Mar;31(6):703-11.

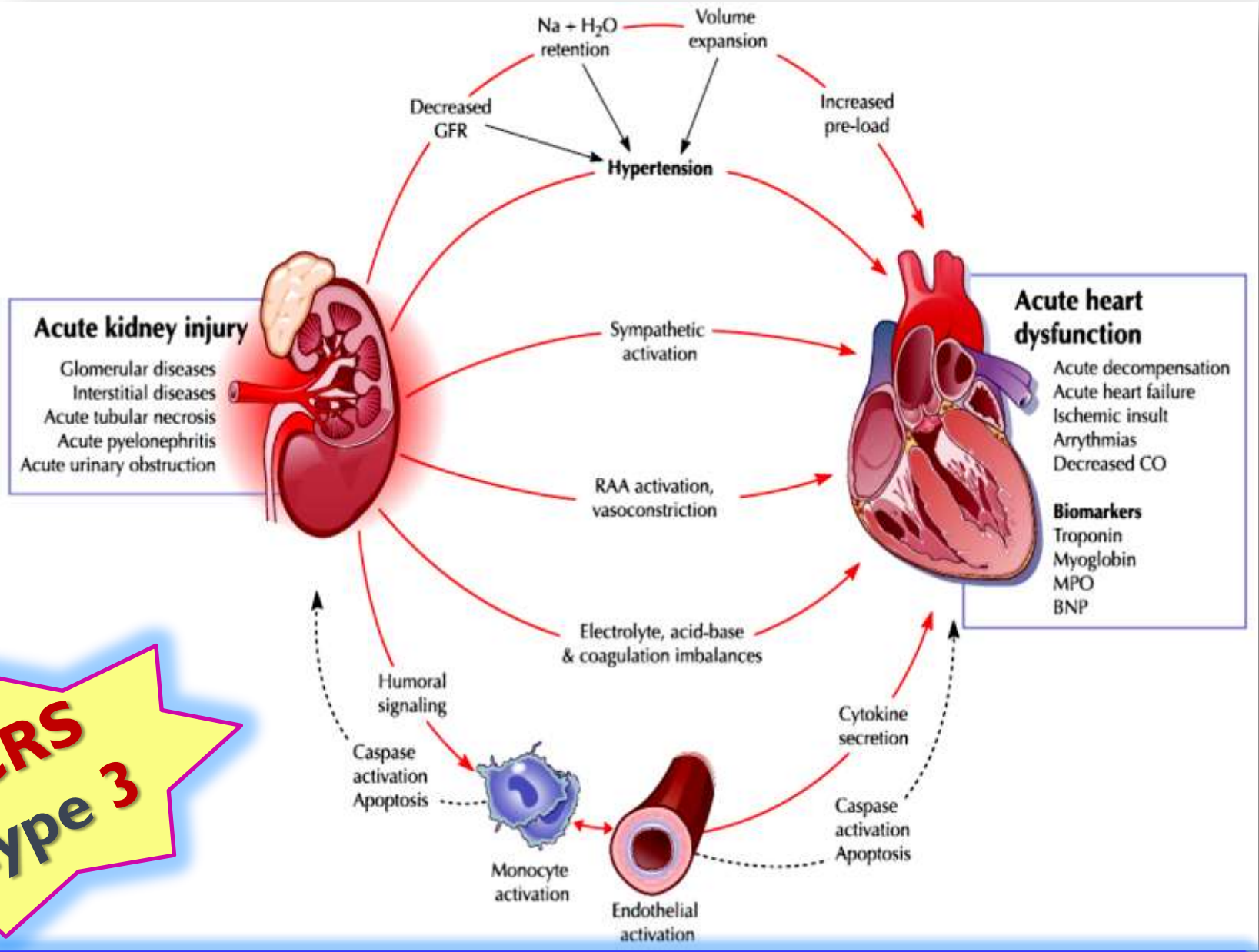


CRS type I

acute worsening of heart function (AHF-ACS) leading to kidney injury and/or dysfunction.

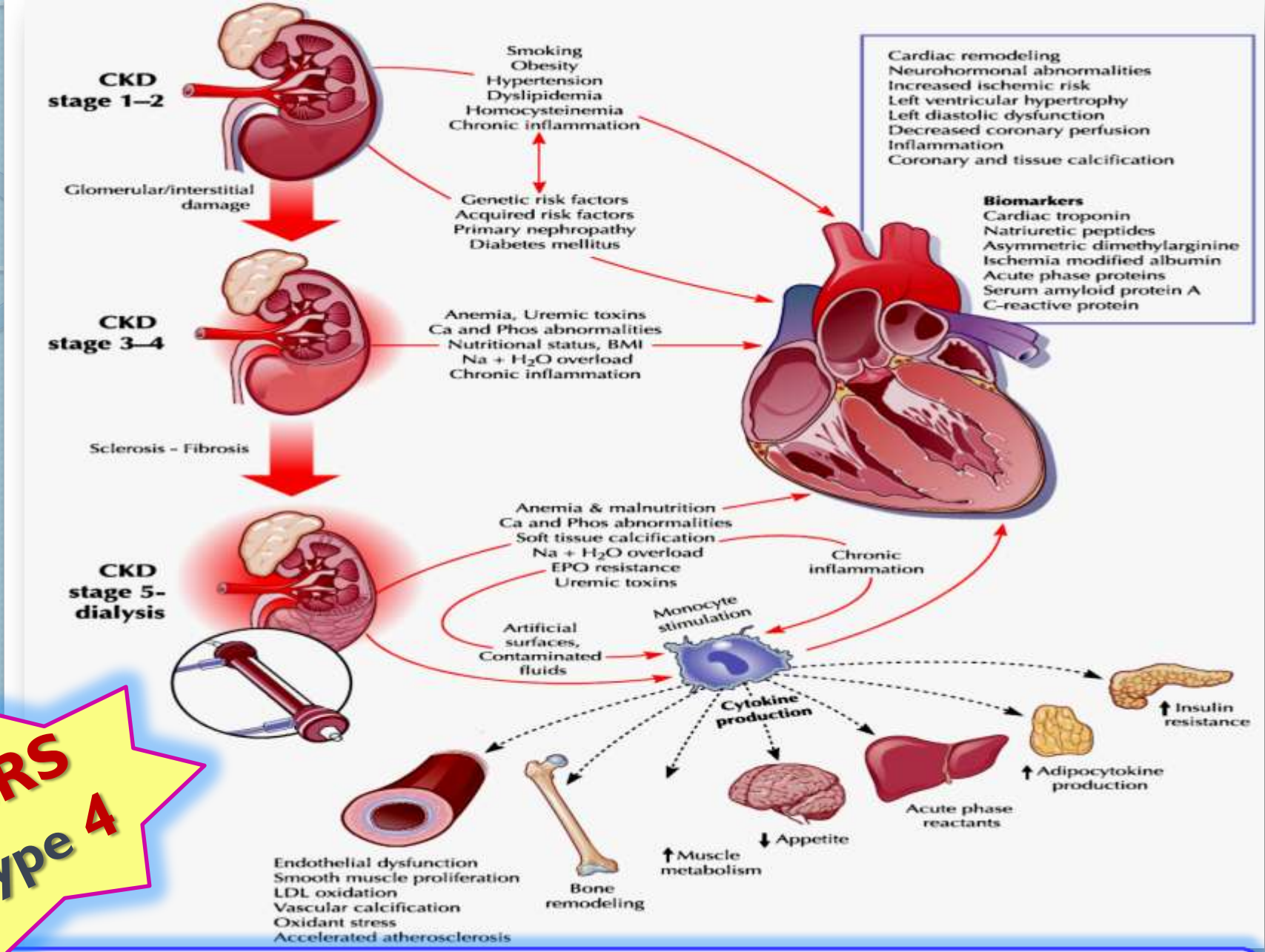


- **Chronic CRS (type 2):** chronic abnormalities in heart function (CHF-CHD) leading to kidney injury and/or dysfunction.



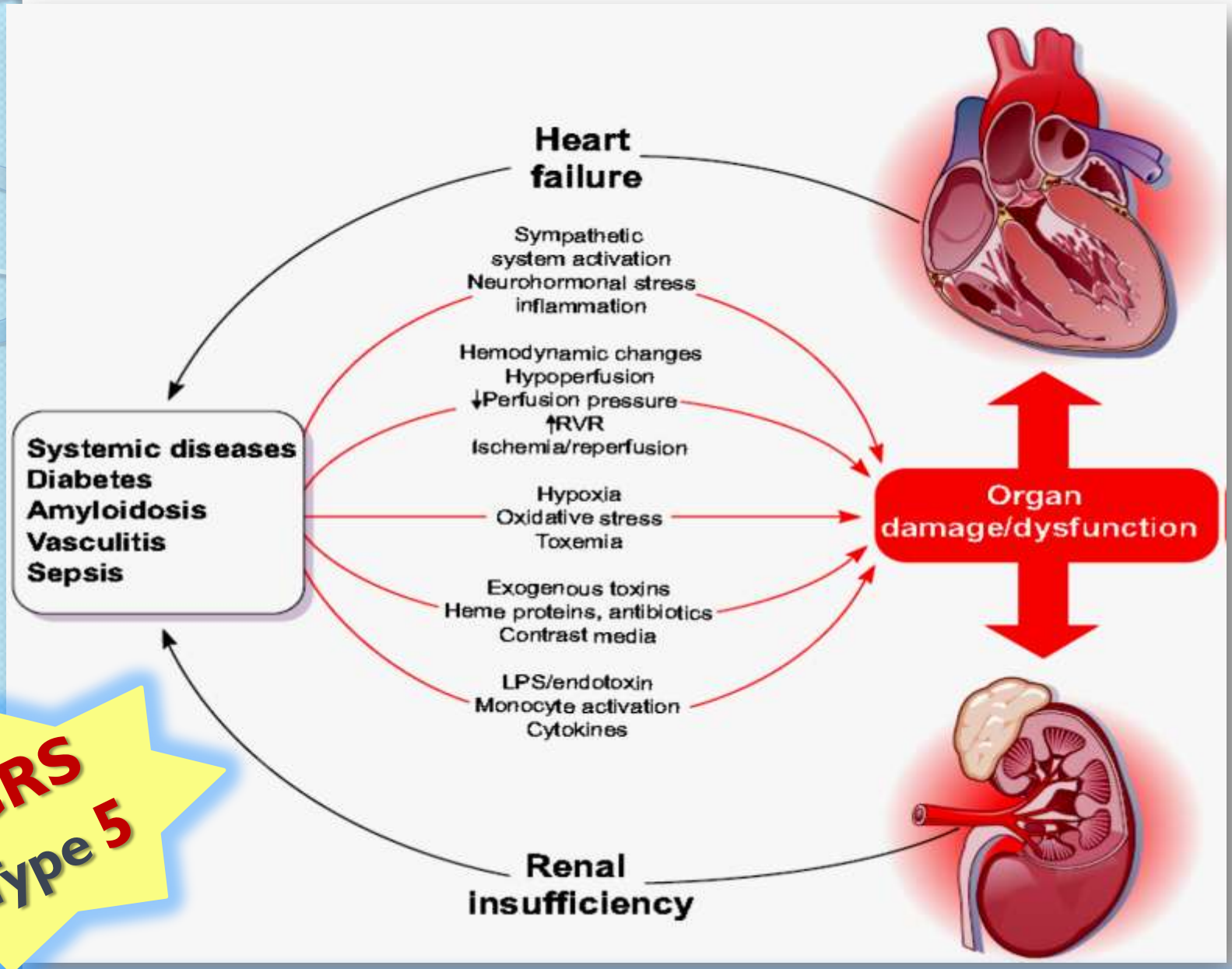
CRS type 3

Acute reno-cardiac syndrome (type 3): acute worsening of kidney function (AKI) leading to heart injury and/or dysfunction..



CRS type 4

Chronic reno-cardiac syndrome (type 4): chronic kidney disease leading to heart injury, disease, and/or dysfunction.



CRS Type 5

Secondary CRS (type 5): systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney.

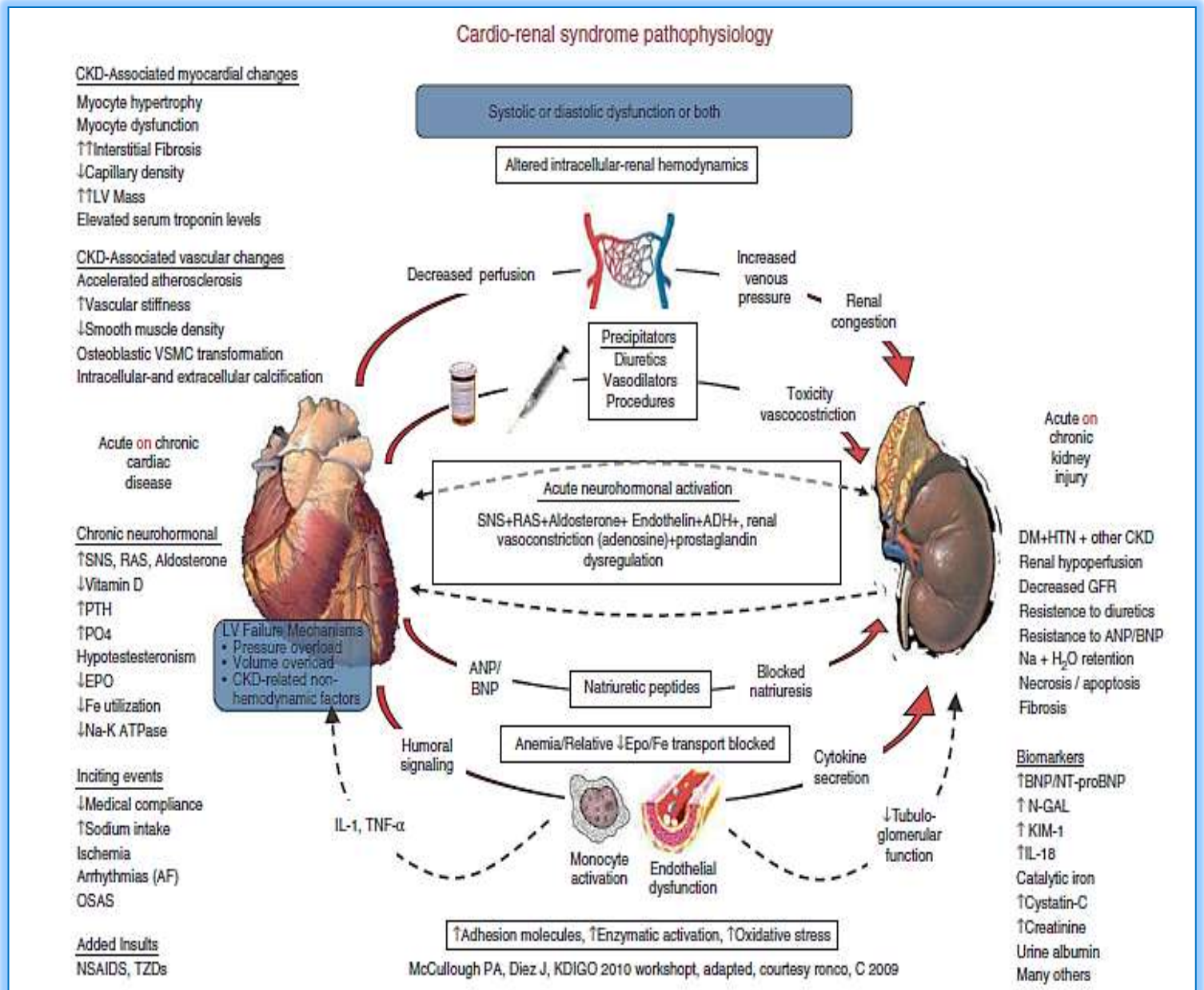
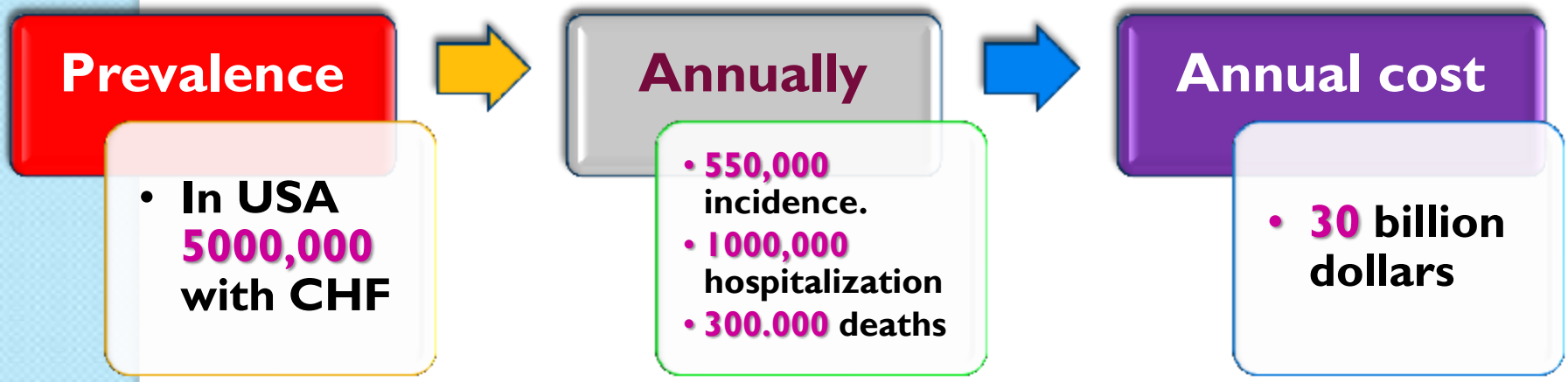


Figure 1 | Cardio-renal syndrome pathophysiology. ADH, antidiuretic hormone; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; DM, diabetes mellitus; EPO, erythropoietin; HTN, hypertension; IL-1, interleukin-1; KIM-1, kidney injury molecule-1; LV, left ventricular; N-GAL, neutrophil gelatinase-associated lipocalin; NSAID, non-steroidal anti-inflammatory drug; OSAS, obstructive sleep apnea syndrome; PTH, parathyroid hormone; SNS, sympathetic nervous system; TNF-α, tumor necrosis factor-α; TZD, thiazolidinediones; VSMC, vascular smooth muscle cell.

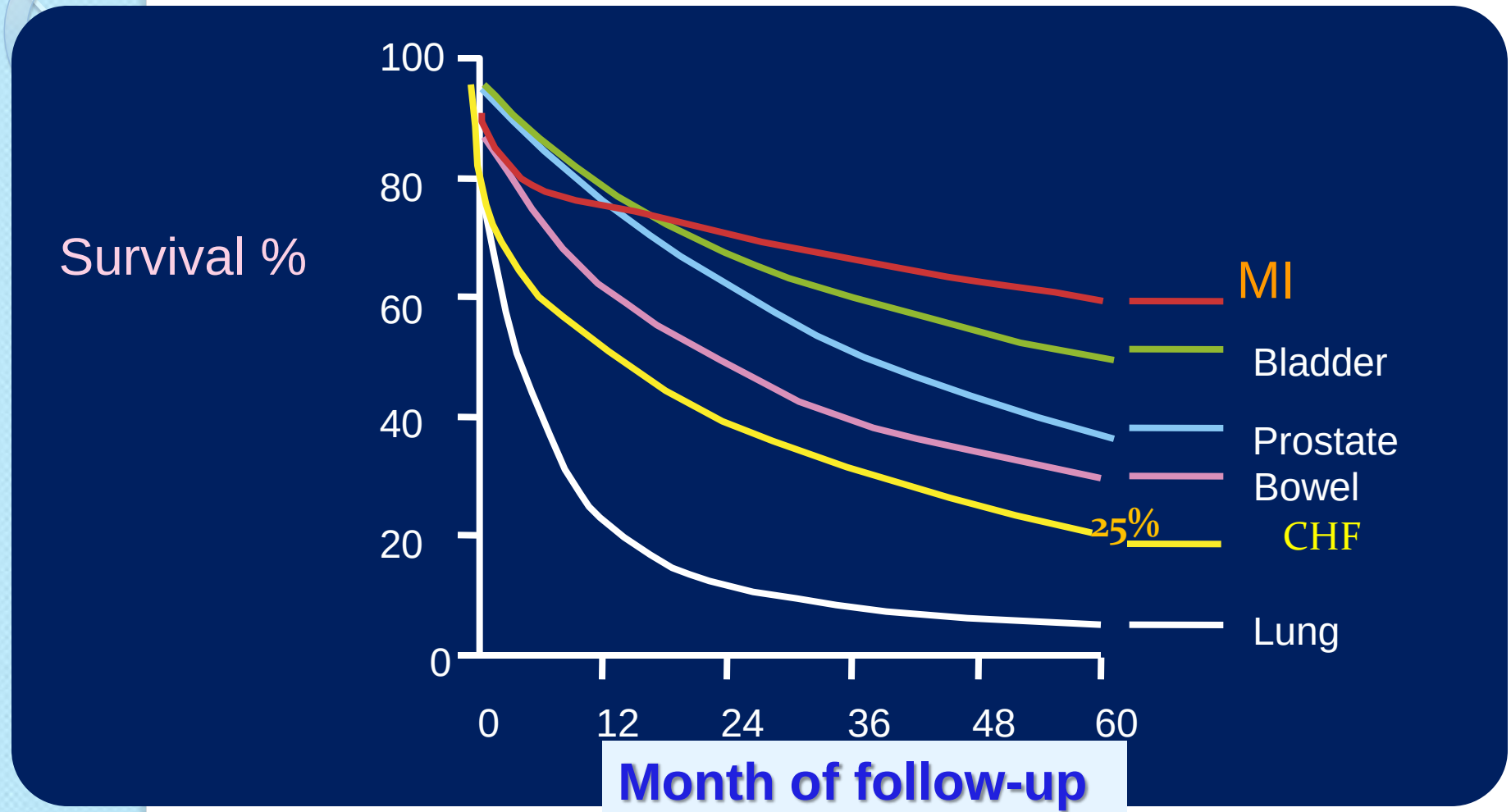
Epidemiology of CHF



Rosamond et al. Heart disease and stroke statistics– 2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007; 115: e69–171

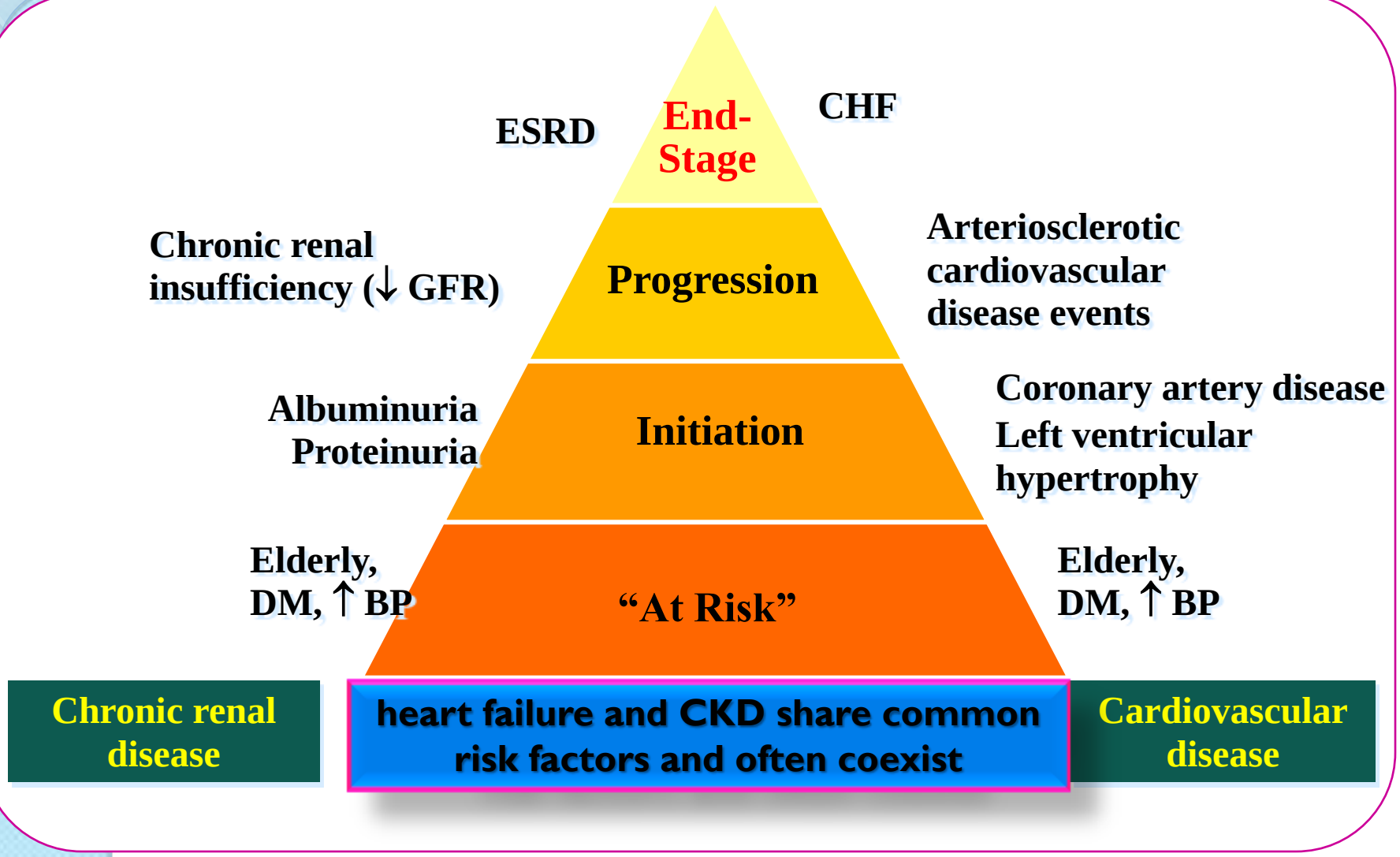
Survival Following Diagnosis

Kosiborod et al. Am J Med. 2003;114:112-119



The 5-year survival for heart failure is about 25%, after the first admission (worse than that for breast or bowel cancer) .

Cardiovascular and renal disease continuum



Adapted from Sarnak and Levey, *Am J Kidney Dis* 2000;35:S117–31.

Serum Creatinine as Biomarker in CRS

versus

Current biomarkers in CRS

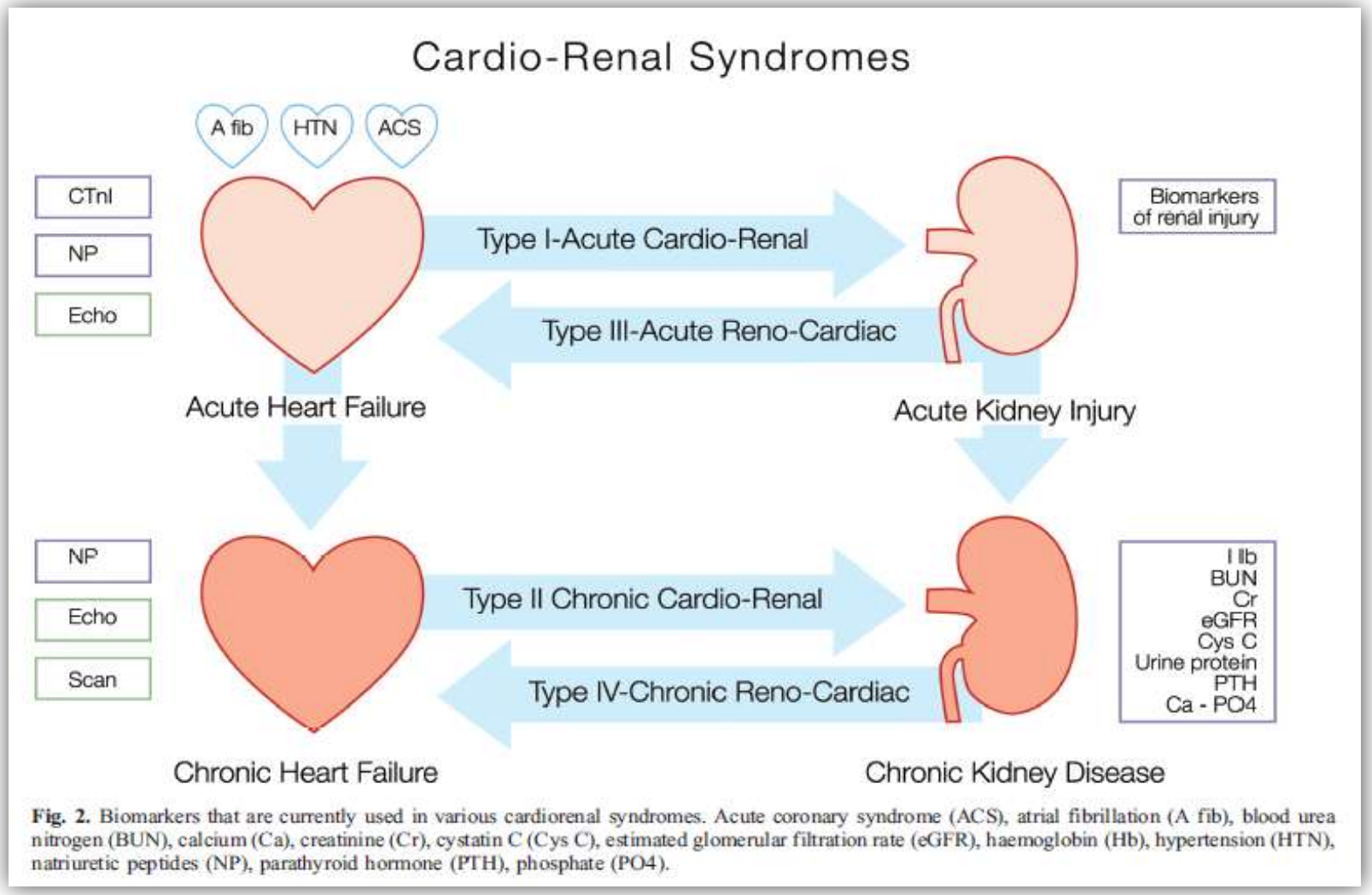


Fig. 2. Biomarkers that are currently used in various cardiorenal syndromes. Acute coronary syndrome (ACS), atrial fibrillation (A fib), blood urea nitrogen (BUN), calcium (Ca), creatinine (Cr), cystatin C (Cys C), estimated glomerular filtration rate (eGFR), haemoglobin (Hb), hypertension (HTN), natriuretic peptides (NP), parathyroid hormone (PTH), phosphate (PO4).

Nephrol Dial Transplant 2011; 26: 62–74

Link between GFR and CVD

- In the Atherosclerosis Risk in Communities (**ARIC**) study of over 15,000 randomly chosen subjects age 45 to 64 years .

Manjunath, et al. J Am Coll Cardiol 2003; 41:47.

Link between CKD->CHF

The risk for CVD starts to increase once the GFR starts to drop below 60 mL/minute/1.73 m2 (1).

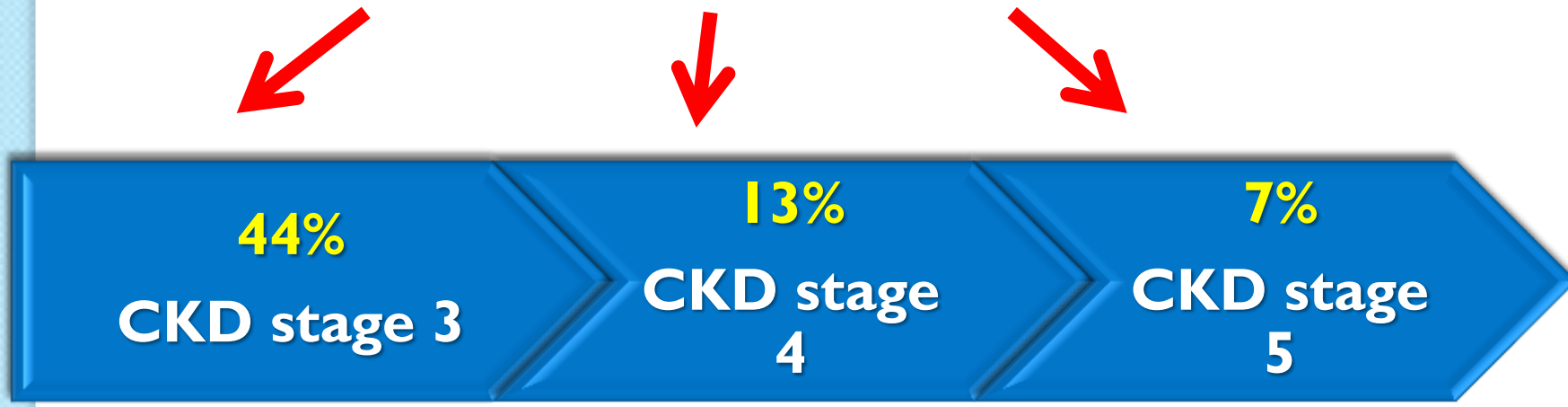
A creatinine increase of ≥ 0.3 mg/dL

- **Predictor of hospital mortality (sensitivity 65%) (specificity 81%)(2).**
- **2.3-day longer length of hospital stay.**
- **33% increased risk for hospital readmission (3).**
- **67%, increased risk of death within 6 months after discharge**

1.Sarnak et al., Circulation. 2003;108:2154-2169 2. Gottlieb et al., *J Card Fail. 2002;8:136–141.*
3. Smith et al., *J Card Fail. 2003;9:13–25.*

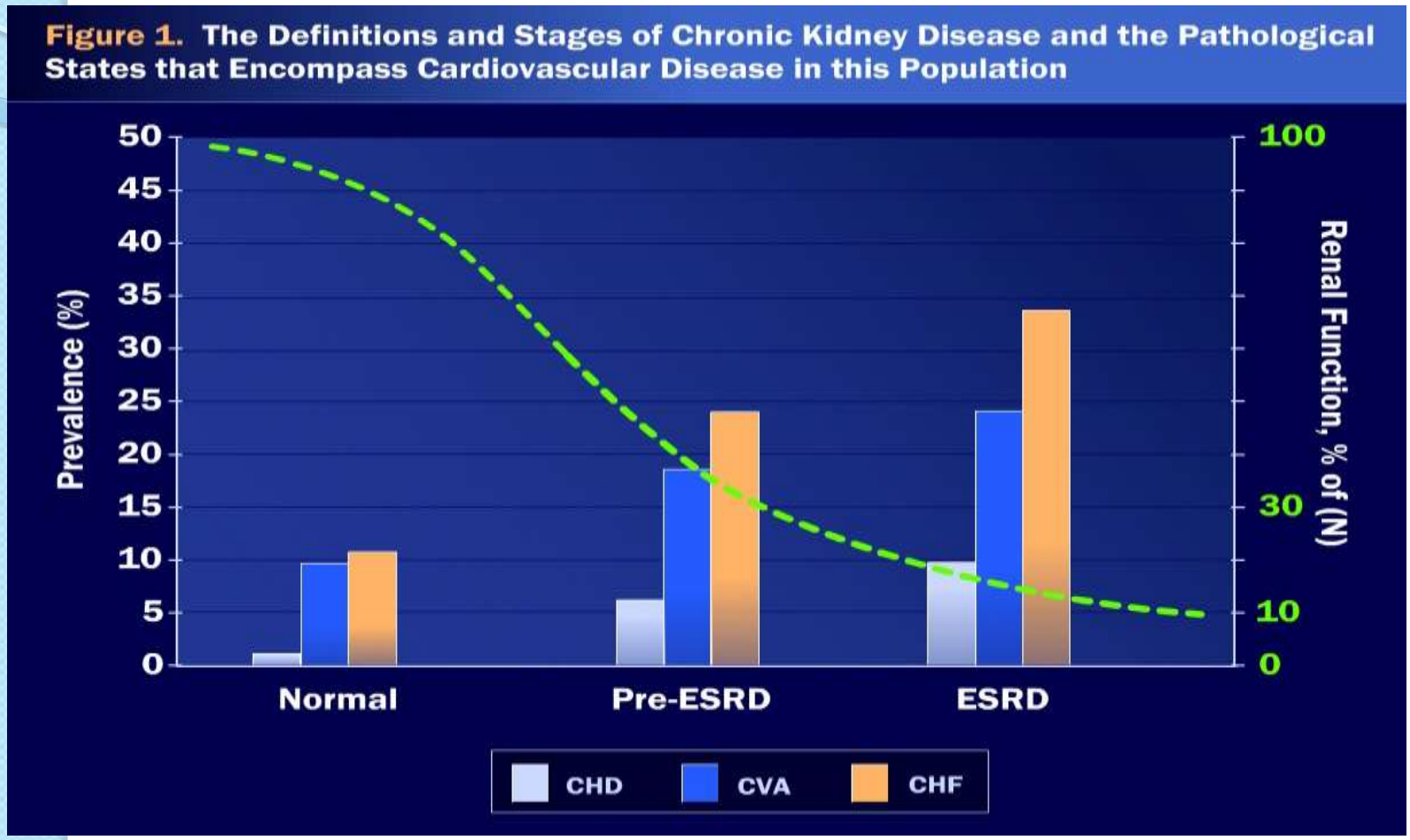
Acute Decompensate Heart Failure National Registry (ADHERE)

64% of patients with CHF has impaired kidney function



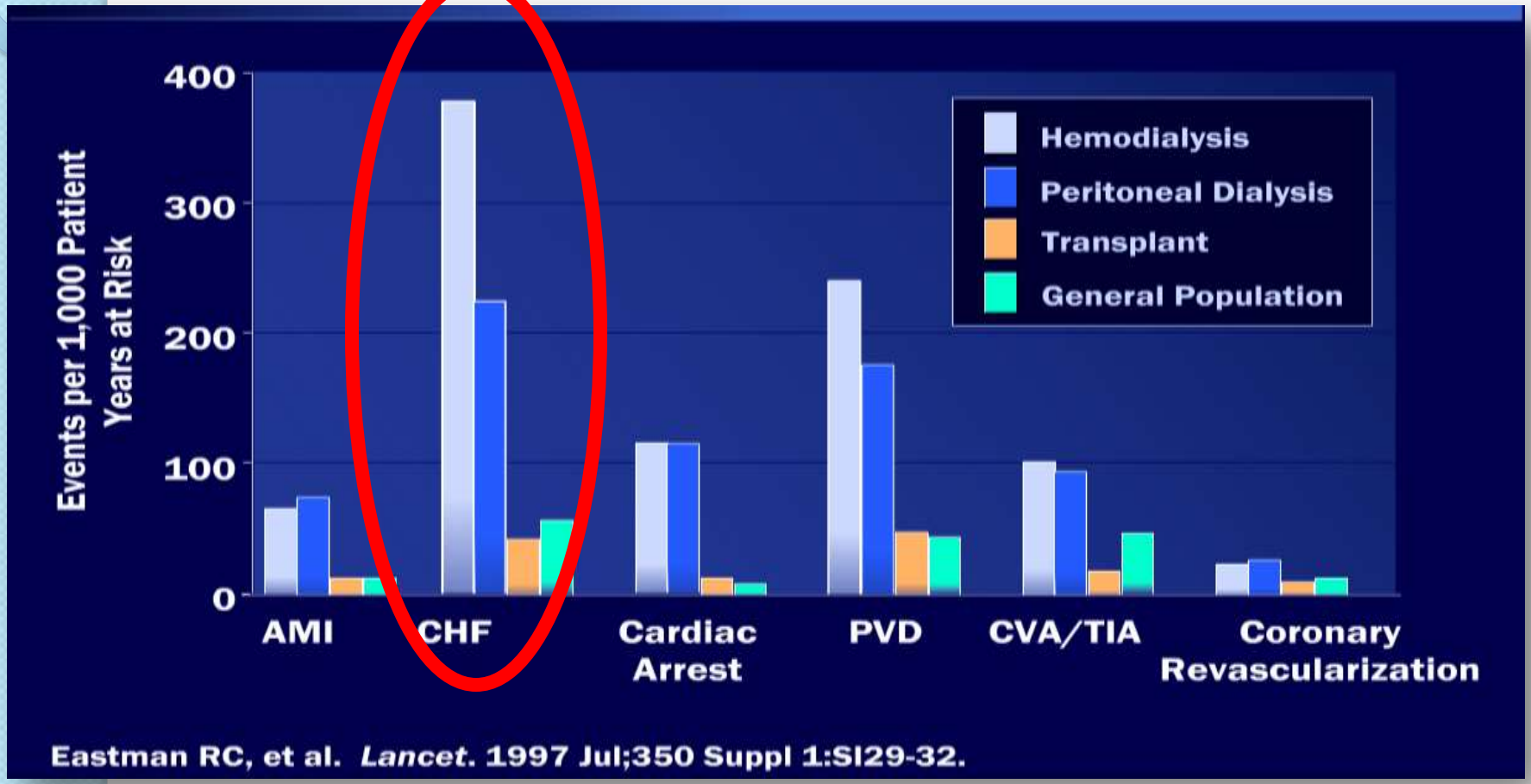
Heywood et al . 2007. J Card Fail 2007; 13: 422–430.O

CHF is the most common Cardiovascular Disease among CKD Stages



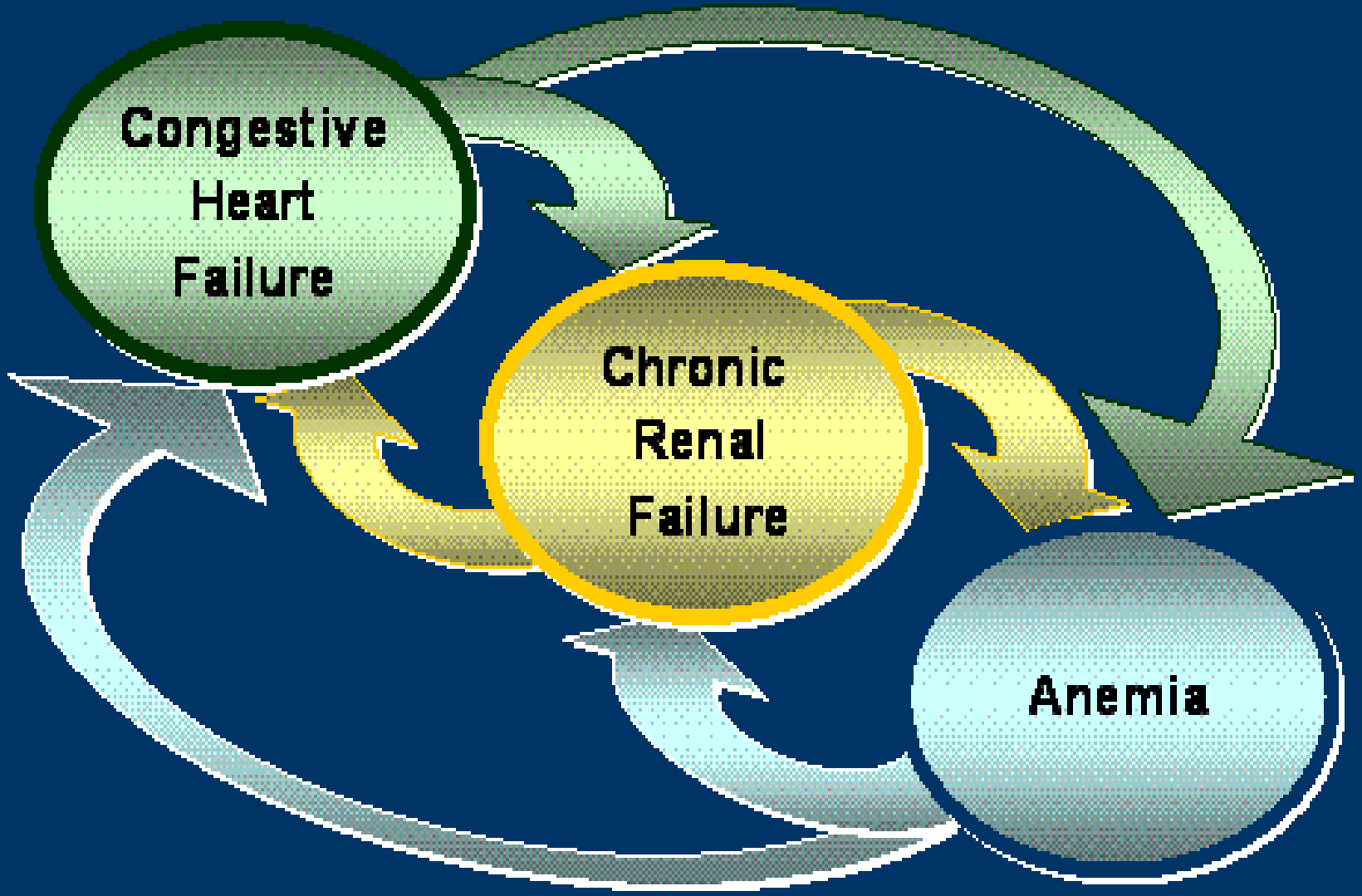
Culleton BF, Larson MG, Wilson PW, et al. *Kidney Int* 1999;56:2214-9.
Levin A, Djurdjev O, Barrett B, et al. *Am J Kidney Dis* 2001;38:1398-407.
U.S. Renal data system, usrds 2002

CV Events in Patients with CKD on renal replacement therapy



Modified from USDR 2002 Report, Cardiovascular Special Studies

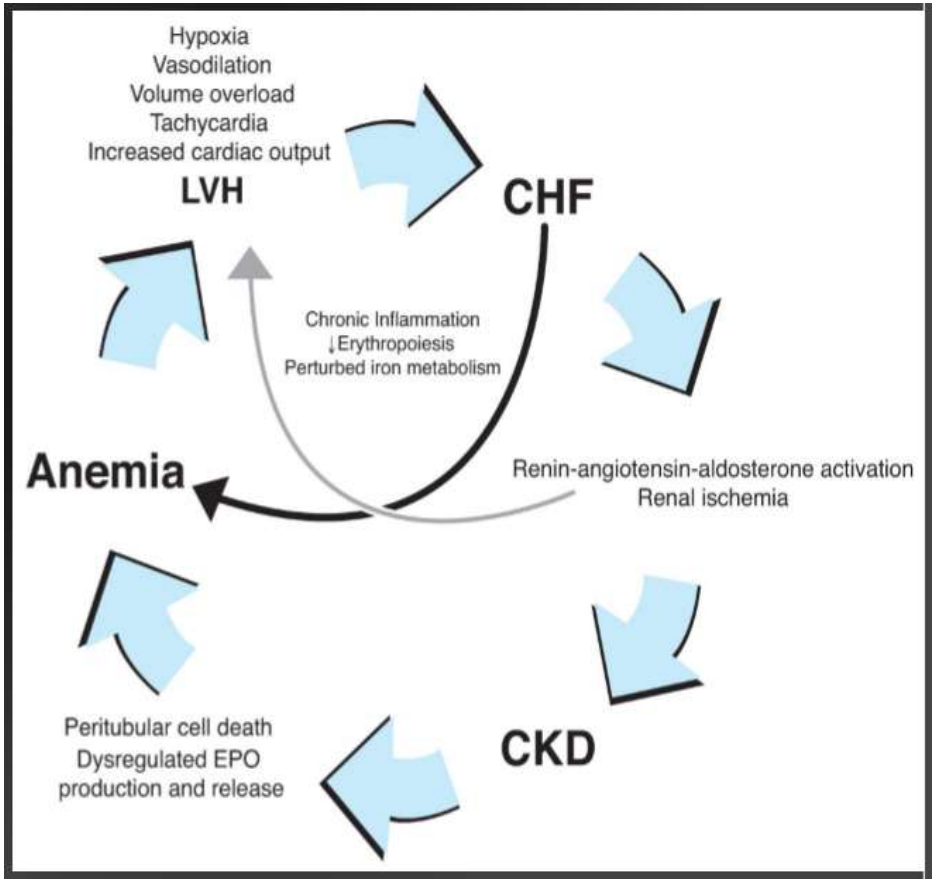
Cardio-Renal Anemia Syndrome



Silverberg. *Eur J Heart Fail.* 2002;4:681.

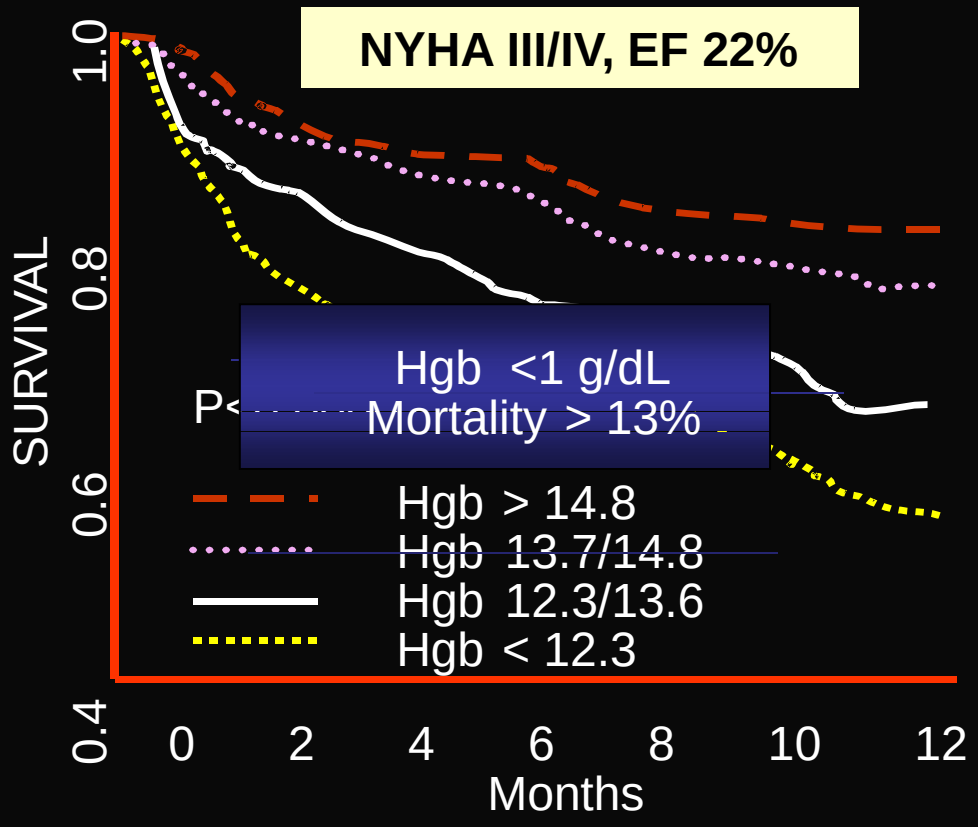
Cardiorenal Anemia Syndrome

The cardiorenal anemia syndrome. Congestive heart failure (CHF) is a cause and consequence of CKD. First, CHF inflames the heart, liver, and vasculature, creating an influx of circulating cytokines that depress erythropoiesis and perturb iron metabolism [44]. Second, CHF directly induces kidney damage, in which GFR can deteriorate by as much as one mL/min/month [45–47]. In response to reduced cardiac output, blood pressure (and renal perfusion) is maintained by activation of the reninangiotensin-aldosterone system. Angiotensin II-mediated renal vasoconstriction and increased metabolic demands of the kidney result in renal ischemia and ultimately tubular cell death [1]. Renal cell death in turn hastens anemia through loss of endocrine function. In addition, aldosterone-induced salt and water retention leads to an increased preload on the heart, which increases its rate in an attempt to increase output.

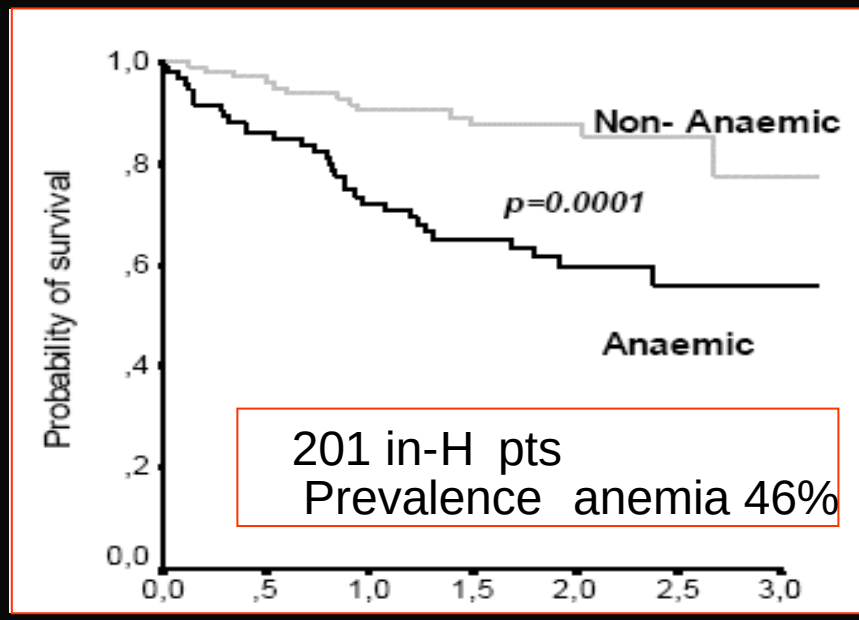


Schmidt and Dalton Osteopathic Medicine and Primary Care 2007 1:14 doi:10.1186/1750-4732-1-14

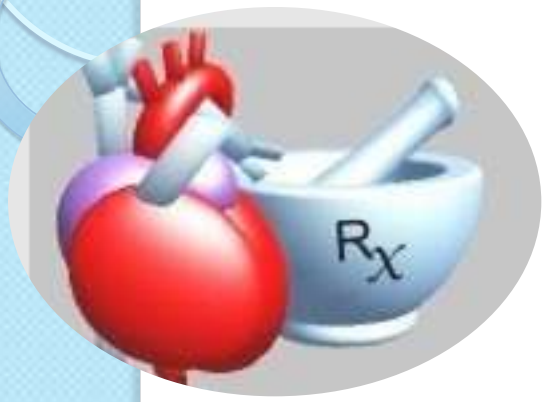
Anemia *and* Prognosis



PRESERVED SYSTOLIC FUNCTION

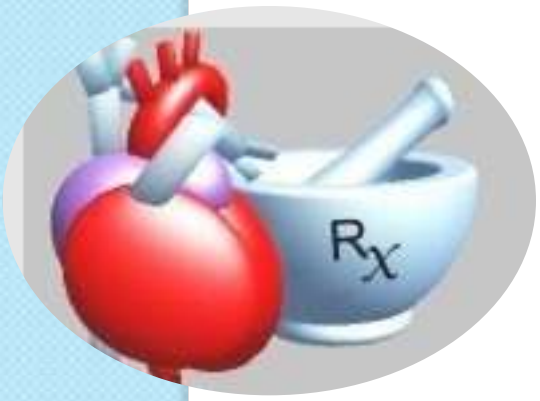


Shamagian et al. Heart on- lineOct. 20



Treatment challenges

Treatment of patients with cardiorenal syndrome



- **Diuretic**.
- Aldosterone antagonists
- Beta-blocker---carvidelol
- Vasodilators.
- ACEIs, ARBs.
- **Ultrafiltration, Dialysis**

Cohen, Anemia and Heart Disease in the Patient With Chronic Kidney Disease: An Expert Interview With Eric Cohen , 2004.
Kosiborod et al., Am J Med. 2003;114:112-119
Cice et al. J Am Coll Cardiol. 2003;41:1438-1444

Diagnosis & Management of Volume Overload in CRS

Nephrologist

Cardiologist

Wet or Dry?

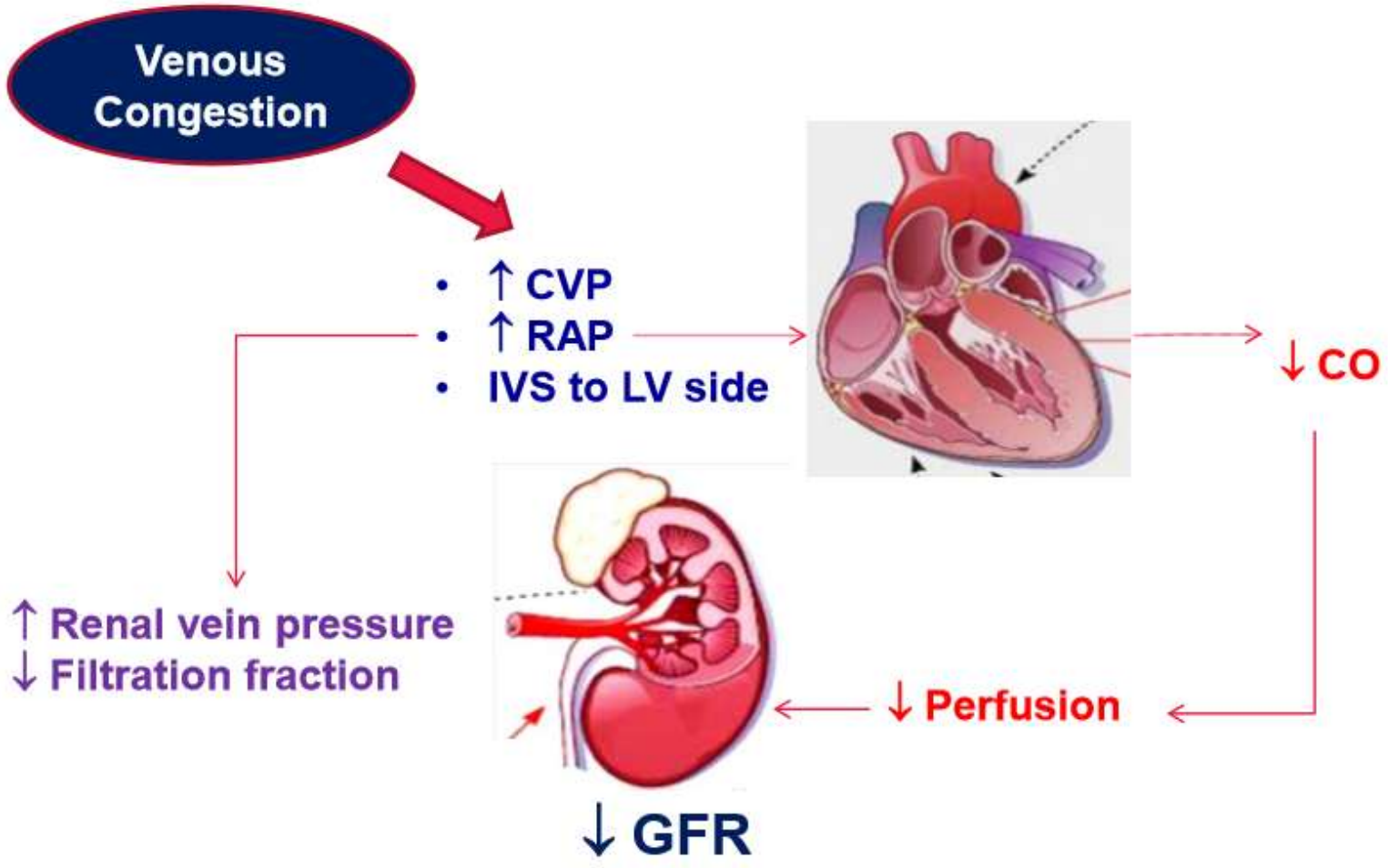
Hypovolemic Cardiorenal Syndrome

- Over diuresed or inter current illness results in volume loss and renal dysfunction
- Often a reluctance to give fluids to HF patients but it may be critical in this situation and time is of the essence to avoid irreversible renal damage

CRS due to high central venous pressure

- Poor renal perfusion due to high central venous pressure
- Usually CVP > 15 mm Hg +/- reduced blood pressure
- Diuretics often held because of worsening renal function.

Mechanisms of worsening renal function in the face of circulatory congestion



Over **90%** of All Hospitalizations for Acutely Decompensated Heart Failure (ADHF) Are Due to Fluid Overload

Aronson. ACC. 2000. .

Acute Volume Management

- Volume overloaded hypertensive patients
- Volume overloaded normotensive patients
- Volume overloaded hypotensive patients
- Preload reduction
- Afterload reduction

Diuretics in CRS

The immediate symptomatic beneficial effects of diuretics are brought about by:

- Improved Pulmonary congestion
- Decreased Ventricular Wall stretch and Ventricular dilatation
- Venodilation leading to immediate reduction in preload (with IV Furosemide)

The Open Urology & Nephrology Journal, 2015, *8*, 45-52

Cardio Renal Syndromes 2015: Is there a Silver Lining to the Dark Clouds?

Jagadish Jamboti[*,1,2]

[1]*Fiona Stanley Hospital, Western Australia 6150, Australia*

[2]*University of Western Australia, Perth, Western Australia, Australia*

Table 2. Major classes of Diuretics used in CRS.

Generic Name	Class	Initial Dose (mg)	Comments
Furosemide (Frusemide)	Loop	80	IV; PO equivalent is~twice the IV dose. Most commonly (ab)used diuretic!
Bumetanide	Loop	0.5	Oral and IV doses are the same
Torsemide	Loop	5-10	Best oral availability
Ethacrynic acid	Loop	50	Used if allergic to furosemide
Hydrochlorothiazide	Thiazide	12.5	PO; Weak diuretic per se-used with frusemide for sequential tubular blockade of Na reabsorption
Metolazone	Thiazide	2.5	Only available orally; high risk of hypokalaemia

Diuretic resistance is a phenomenon of diminished diuretic effect prior to achieving the therapeutic goal of edema relief.

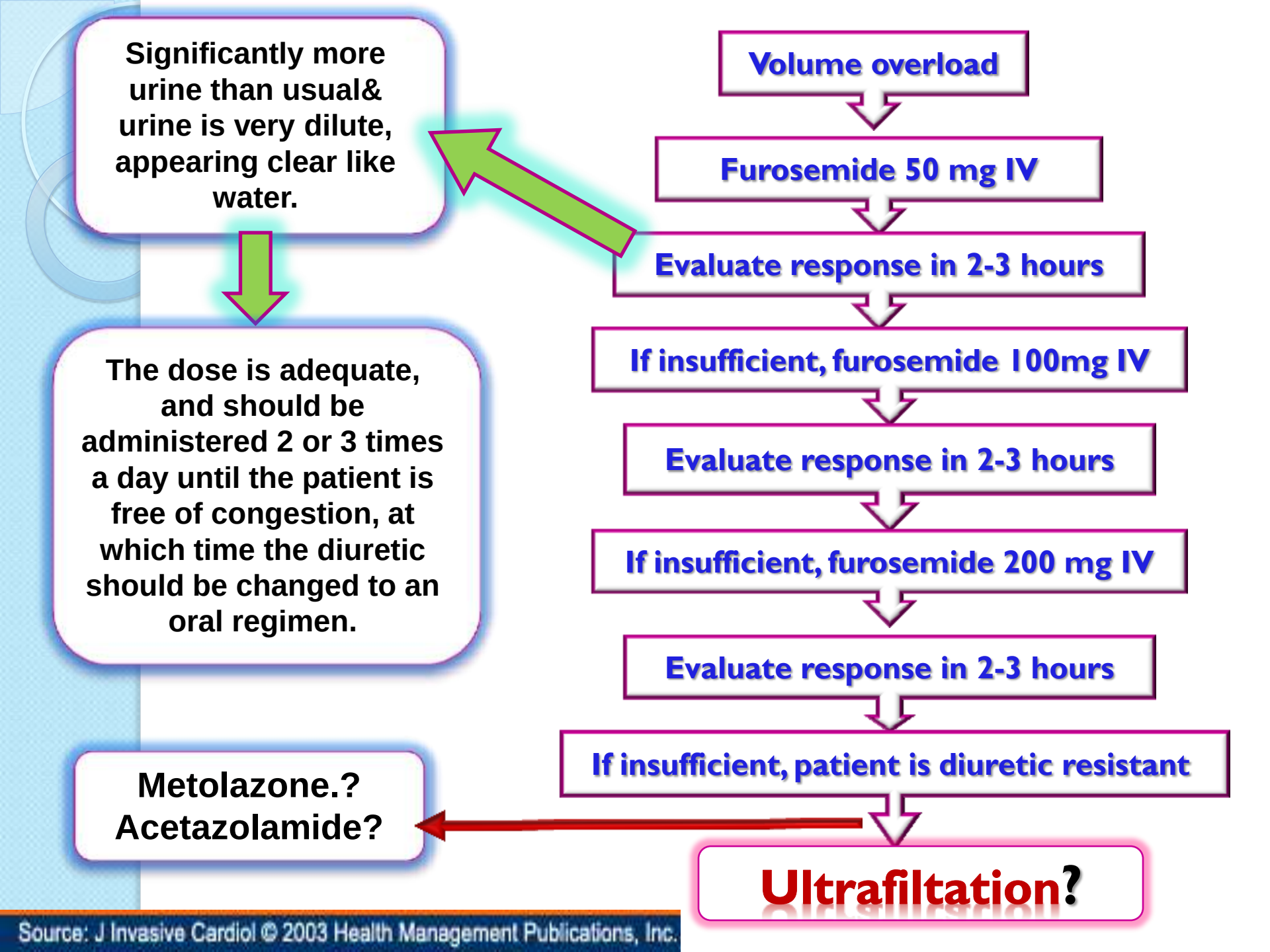
Table 3. Diuretic resistance in ADHF and CRS.

1. Failure of diuretics to reach tubular site of action
- Decreased G.I. absorption (Gastro Intestinal edema)
- Decreased secretion into tubular lumen (↓ GFR)
2. Compensatory Mechanisms
- RAAS, SNS ↑*Na reabsorption in PCT*
3. Post dose Compensatory retention of Na
4. Tubular adaptation
- Chronic Loop diuretic use- *RAAS stimulation leading to Hypertrophy and hyperplasia of DCT*
5. ↑Aldosterone in CD

Diuretic resistance is a phenomenon of diminished diuretic effect prior to achieving the therapeutic goal of edema relief.

Table 3. Diuretic Resistance Treatment Approaches

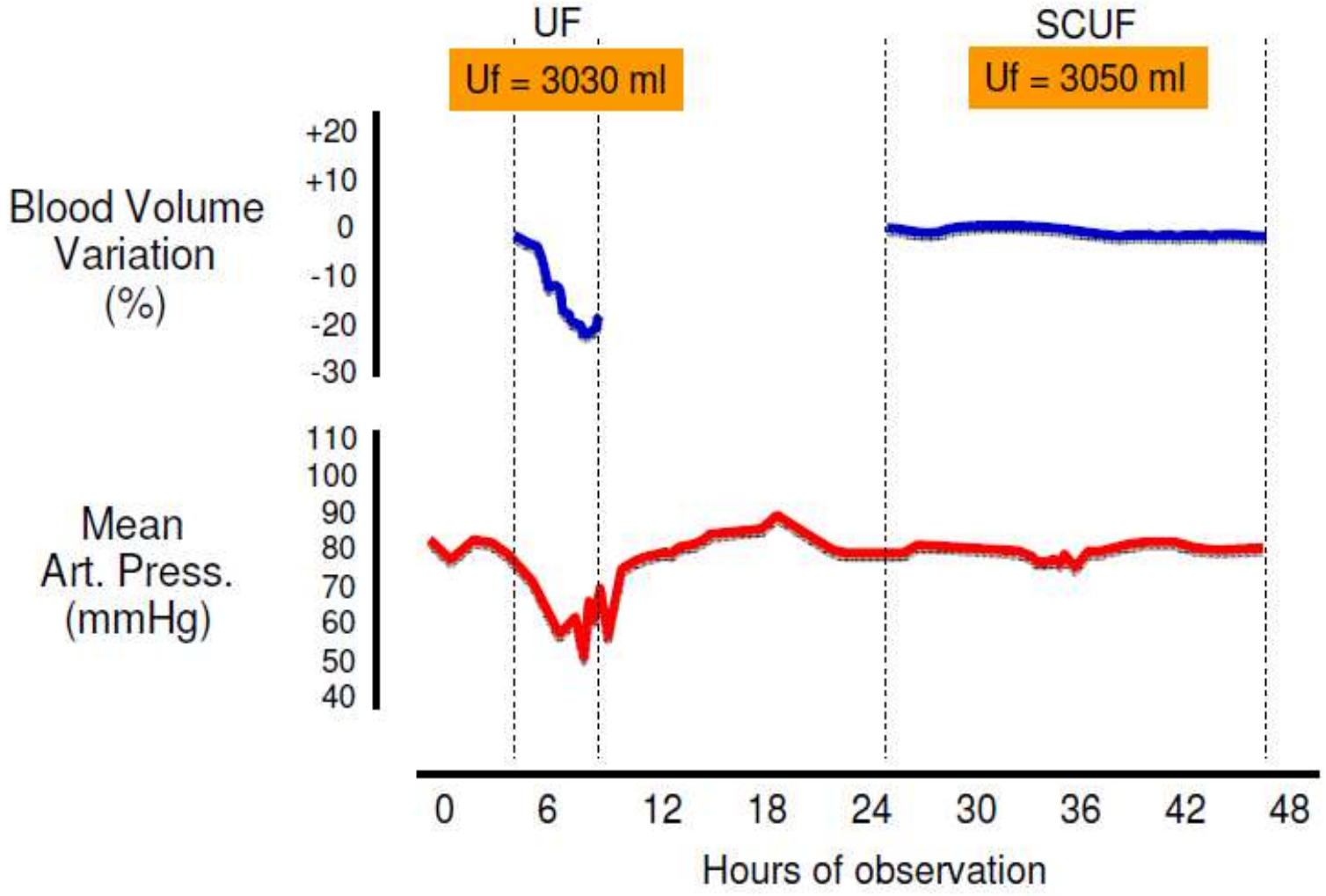
- Increase dose or frequency of diuretic
  - Continuous infusion more effective than bolus dosing
- Change route of administration to IV
  - IV route may overcome absorption issues
- Add a second diuretic of a different class (i.e., thiazide)
  - Decreases sodium reabsorption in the distal convoluted tubule
- Add an inotropic agent (i.e., dopamine, dobutamine)
  - Increases cardiac output, presents more volume to the kidneys
- Discontinue interacting medications (i.e., NSAIDs)
- Restrict sodium and water
- Consider ultrafiltration if inadequate response to diuretic therapy persists



Fluid Removal by RRT

- **Intermittent**:
  - IHD
- **CRRT**
  - CVVH, SCUF
  - CVVHD, CVVHDF
  - SLEDD
  - PD: APD, CCPD

Hemodynamic Response of CRRT



Aquapheresis Therapy

- Therapy to **safely achieve euvolemia** (dry weight)
- Uses a simplified form of ultrafiltration

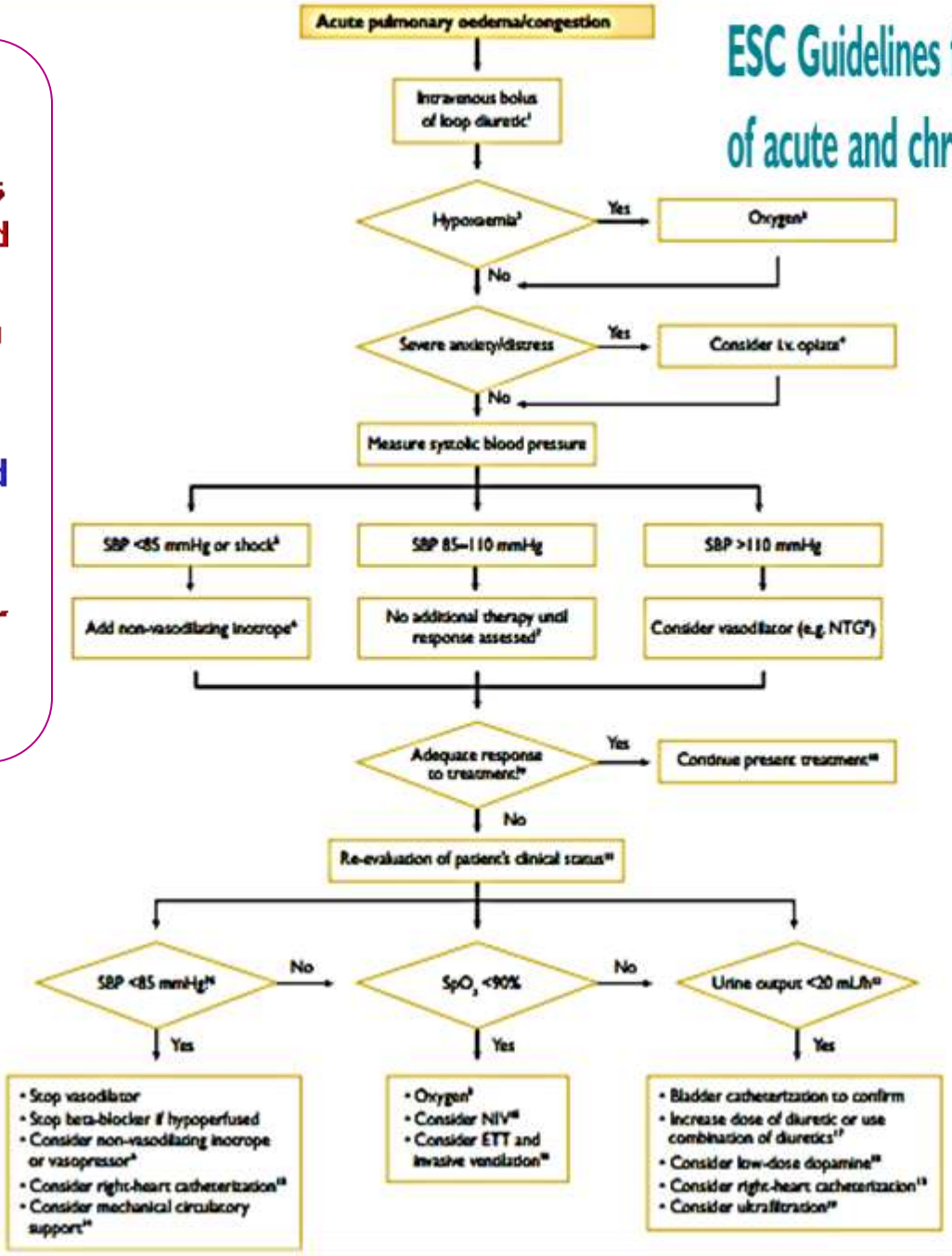
- Quick and easy device setup:	less than 10 mins
- Low blood flow:	20-40 mL/min
- Low blood volume:	**33 mL**
- Precise fluid removal rates:	10-500 mL/hour

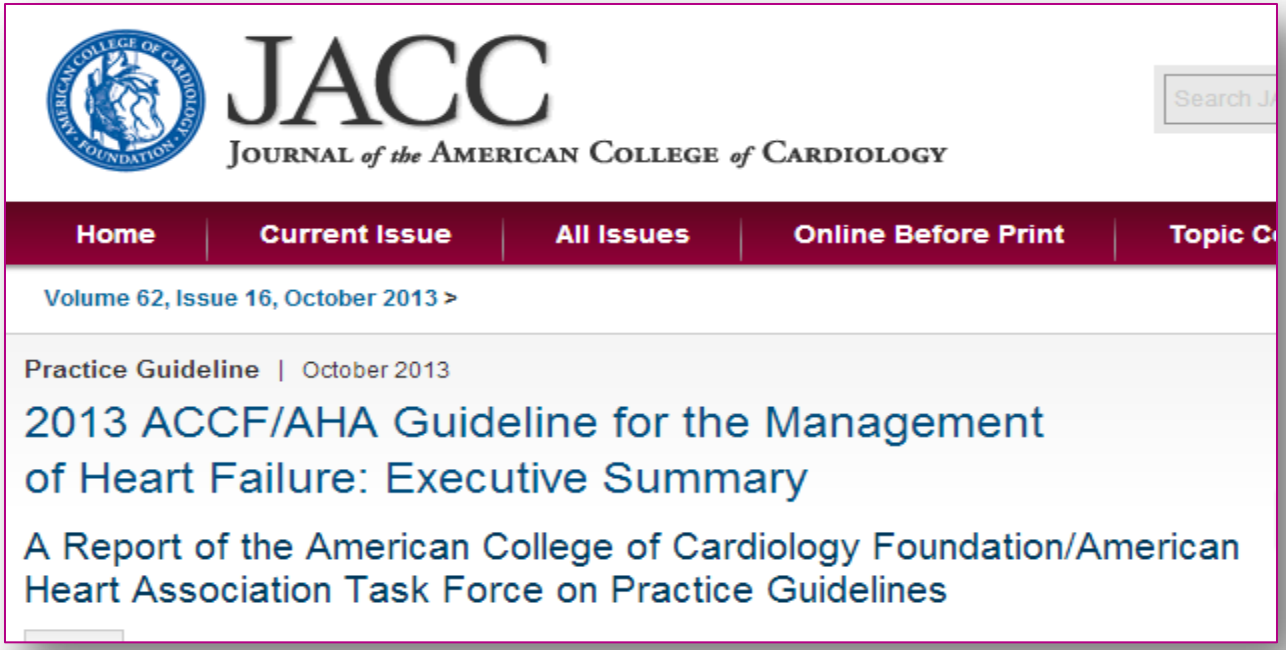
- **Inpatient** or **outpatient** settings
  - ICU, CCU, MICU, telemetry, stepdown, observation, ED, outpatient clinics
- **Peripheral** or **central** venous access
  - Flexible access sites and catheters
- Diverse physician prescription
- **No clinically significant impact on electrolyte balance, blood pressure or heart rate**

Think of it as a "mechanical diuretic"...

Venovenous isolated ultrafiltration is sometimes used to remove fluid in patients with HF, although is usually reserved for those unresponsive or resistant to diuretics

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012





7.4 Renal Replacement Therapy—Ultrafiltration

Class IIb

1. Ultrafiltration may be considered for patients with obvious volume overload to alleviate congestive symptoms and fluid weight(319). *(Level of Evidence: B)*
2. Ultrafiltration may be considered for patients with refractory congestion not responding to medical therapy. *(Level of Evidence: C)*

Drugs

- **Aldosterone** receptor antagonists: is controversial, cannot be recommended in dialysis patients with heart failure.
- **Digoxin** — is challenging since the therapeutic-to-toxic ratio may be narrow.
- Treatment of **anemia** with target 10.5 to 11 improve survival.

Ritz, et al., Congestive heart failure due to systolic dysfunction: the Cinderella of cardiovascular management in dialysis patients. Semin Dial 2002; 15:135.

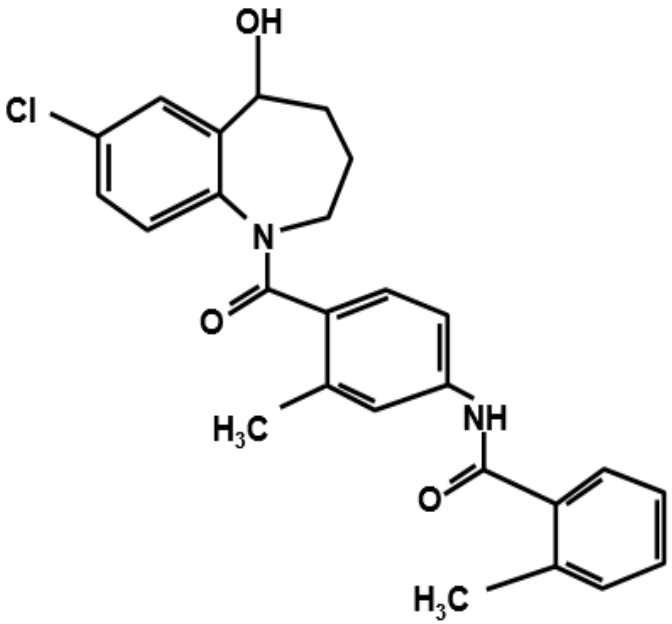
Drugs

- **Carvidelol**.
- **ACEI**: In the randomized FOSIDIAL trial, there was a no significant trend toward fewer cardiovascular events with fosinopril.
- **ARB** is less effect than ACEIs, ARBs may improve cardiovascular outcomes in dialysis patients.

Cice, et al. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy. A prospective, placebo-controlled trial. J Am Coll Cardiol 2003; 41:1438.
Zannad, et al. Prevention of cardiovascular events in end-stage renal disease: Results of a randomized trial of fosinopril and implications for future studies. Kidney Int 2006; 70:1318.
Knoll, et al. Renin-angiotensin system blockade and the risk of hyperkalemia in chronic hemodialysis patients. Am J Med 2002; 112:110.

AVP-R Antagonist – Tolvaptan

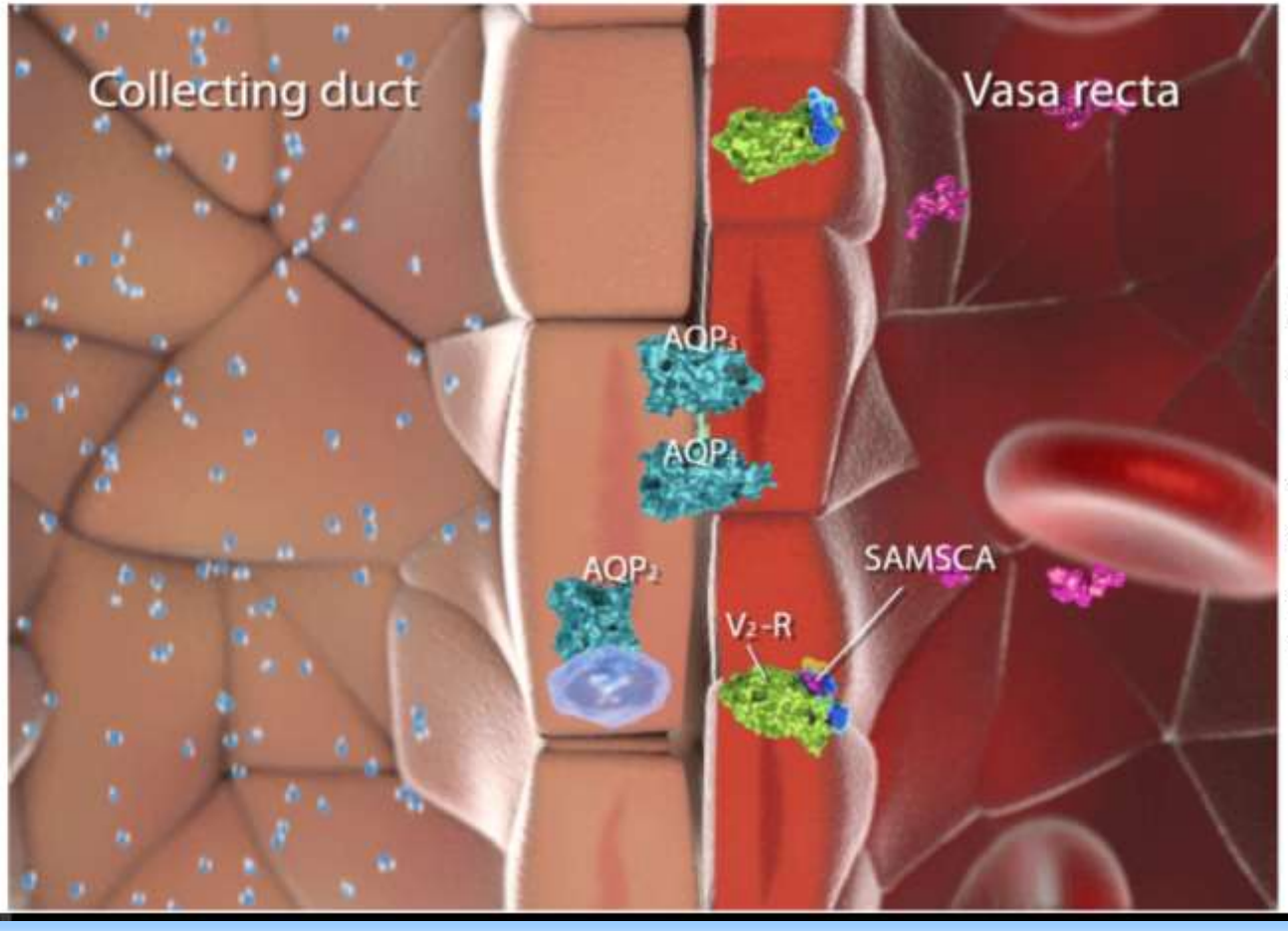
- Mechanism: inhibition of AVP V2 renal receptors in collecting ducts
- Effect: water excretion while sparing electrolytes
- Tolvaptan is the only one currently approved in North America



Tolvaptan

Hussain SM, et al. Expert Opin Pharmacother. 2007;8:2729-2741.

Samsca® (Tolvaptan) Mechanism of Action



Blocking V2-R
↓cAMP

↓ Aquaporin water channels
↓ Free water reabsorption

Journal of Nephrology & Therapeutics

Kulkarni, J Nephrol Ther 2016, 6:1
http://dx.doi.org/10.4172/2161-0959.1000233

Review Open Access

Cardio Renal Syndrome

Manjunath Kulkarni DM*
Department of Nephrology, Father Muller Medical College, Mangalore, India

- **Investigational therapies:** Vasopressin receptors antagonist and adenosine A1receptor antagonists are two classes of drugs which may be of utility in future.
- Tolvaptan, a selective vasopressin 2 receptor antagonist, produces a water diuresis, not a salt diuresis. The EVEREST Outcome trial looked into the effect of tolvaptan on cardiovascular outcomes and decongestion in patients with acute HF. Tolvaptan had no effect on the co-primary end points of all-cause mortality or HF hospitalization. However, there were significant benefits in secondary end points including an increase in urine output, resulting in reduced dyspnea and edema and an increase in serum sodium. Further trials evaluating the role of tovaptan for the management of the CRS should help indefining the use of these drugs

Journal of Nephrology & Therapeutics

Kulkarni, J Nephrol Ther 2016, 6:1
http://dx.doi.org/10.4172/2161-0959.1000233

Review Open Access

Cardio Renal Syndrome

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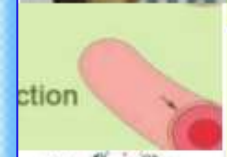
- Selective adenosine A1 receptor antagonist like rolofylline can increase GFR and promote a diuresis by inhibiting the action of adenosine of afferent arteriole. In the PROTECT trial, 2033 patients hospitalized with HF and impaired renal function were randomly assigned to the rolofylline or to placebo [27].
- During the study period, there was no difference between the groups in cardiovascular outcomes or in the rate of persistent worsening of renal function.
- Rolofylline therapy was associated with a higher rate of neurologic events (seizure and stroke). Given the results of this trial, the role of rolofylline is yet undetermined.

Clinical Profiles of the Cardiorenal Syndrome



Etiology	Fluid Status	CO	SVR	Treatment
Too Dry	Dry	Low	N or high	Fluids, stop diuretics
Too Wet (high CVP)	**Wet**	**N**	**N**	**Diuretics+/- aquaretics, ultrafiltration**
Too Clamped Down!!!	Wet or N	Low	High	ACEI, Nitroprusside, Nesiritide
Vasodilated	N or wet	N or high	Low	Stop vasodilators, Pressers, Vasopressin Inotropes
No Pump!!!	Wet / -	Low	N	Inotropes, Vasopressors Balloon Pump LVAD
Intrinsic Renal Disease/Diuretic Resistance	Wet	N	N	Diuretics, ultrafiltration

Journal of Nephrology & Therapeutics

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Summarizes the management of cardiorenal syndrome

Type 1 cardiorenal syndrome	Specific treatment directed towards the precipitating event. General supportive measures: maintain oxygenation, relieve pain and pulmonary congestion, treat arrhythmias appropriately, differentiate left from right heart failure, treat low cardiac output or congestion; avoid nephrotoxins and closely monitor kidney function.
Type 2 cardiorenal syndrome	Treat CHF according to guidelines Exclude precipitating pre-renal AKI factors (hypovolaemia and/or hypotension), Adjust therapy accordingly and avoid nephrotoxins, while monitoring renal function and electrolytes Extracorporeal ultrafiltration and dialysis may be required in cases which do not respond to above measures.
Type 3 cardiorenal syndrome	Specific management for underlying aetiology. Early renal replacement therapy should be considered especially if diuretic resistant.
Type 4 cardiorenal syndrome	Look for reversible causes like hypovolemia and use of Nephrotoxic drugs. Follow KDOQI guidelines for CKD management. Treat heart failure according to guidelines. Consider early renal replacement support
Type 5 cardiorenal syndrome	Specific treatment according to etiology.

Conclusion

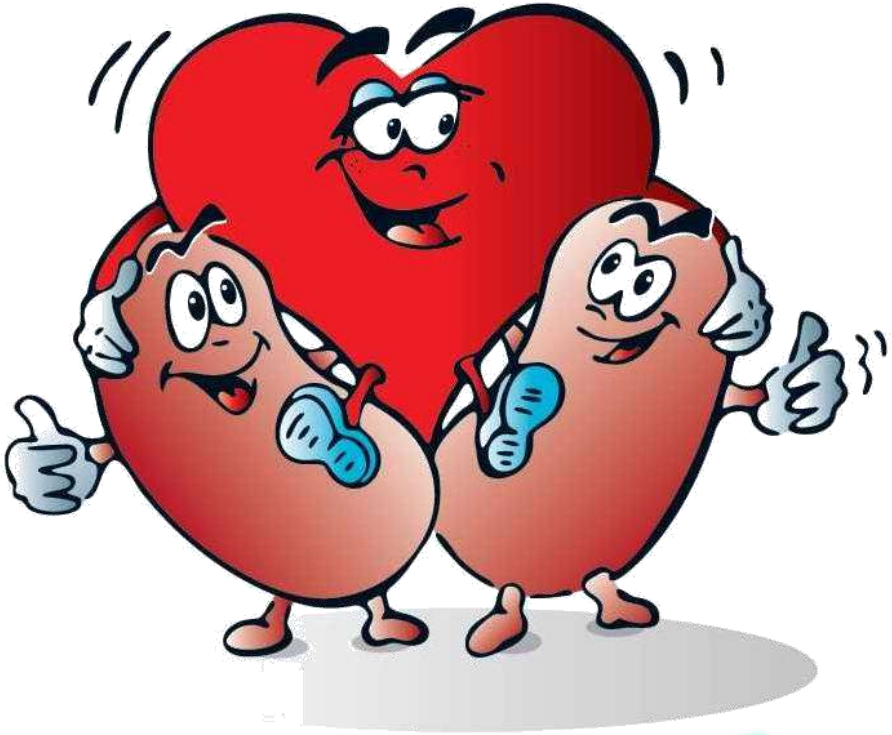
- CRS is a common and has impacted on morbidity and mortality .
- The management of the cardio renal syndrome remains a challenge in spite of the advances in medical therapy and novel agents.
- Early management of CRS in multidisciplinary team approach will improve outcome .

Conclusion

- Treatment of CRS is more challenging in HD.
- Heart-kidney transplantation —most appropriate for selected dialysis patients with severe irreversible cardiac dysfunction.
- Individualizations should be considered.
- It is hoped that new and effective therapies will be identified for the treatment and prevention of this challenging syndrome


INNOVATION
SUCCESS
EVALUATION
DEVELOPMENT
GROWTH
SOLUTION
PROGRESS
MARKETING
TEAMWORK

Thank YOU



Thank you

The Open Urology & Nephrology Journal, 2015, *8*, 45-52

Cardio Renal Syndromes 2015: Is there a Silver Lining to the Dark Clouds?

Jagadish Jamboti[*,1,2]

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Table 1. Cardio-renal syndrome: the plethora of neurohormonal activation.

Cardio-Renal Syndrome: *The Plethora of Neurohormonal activation*	
Vasoconstrictors	***Vasodilators***
SNS	Natriuretic peptide systems (BNP/ANP)
RAAS	Urocortin / Urotensin
Vasopressin	Prostaglandins
Endothelin	Nitric Oxide
Adenosine	Adrenomedulllin
	Relaxin

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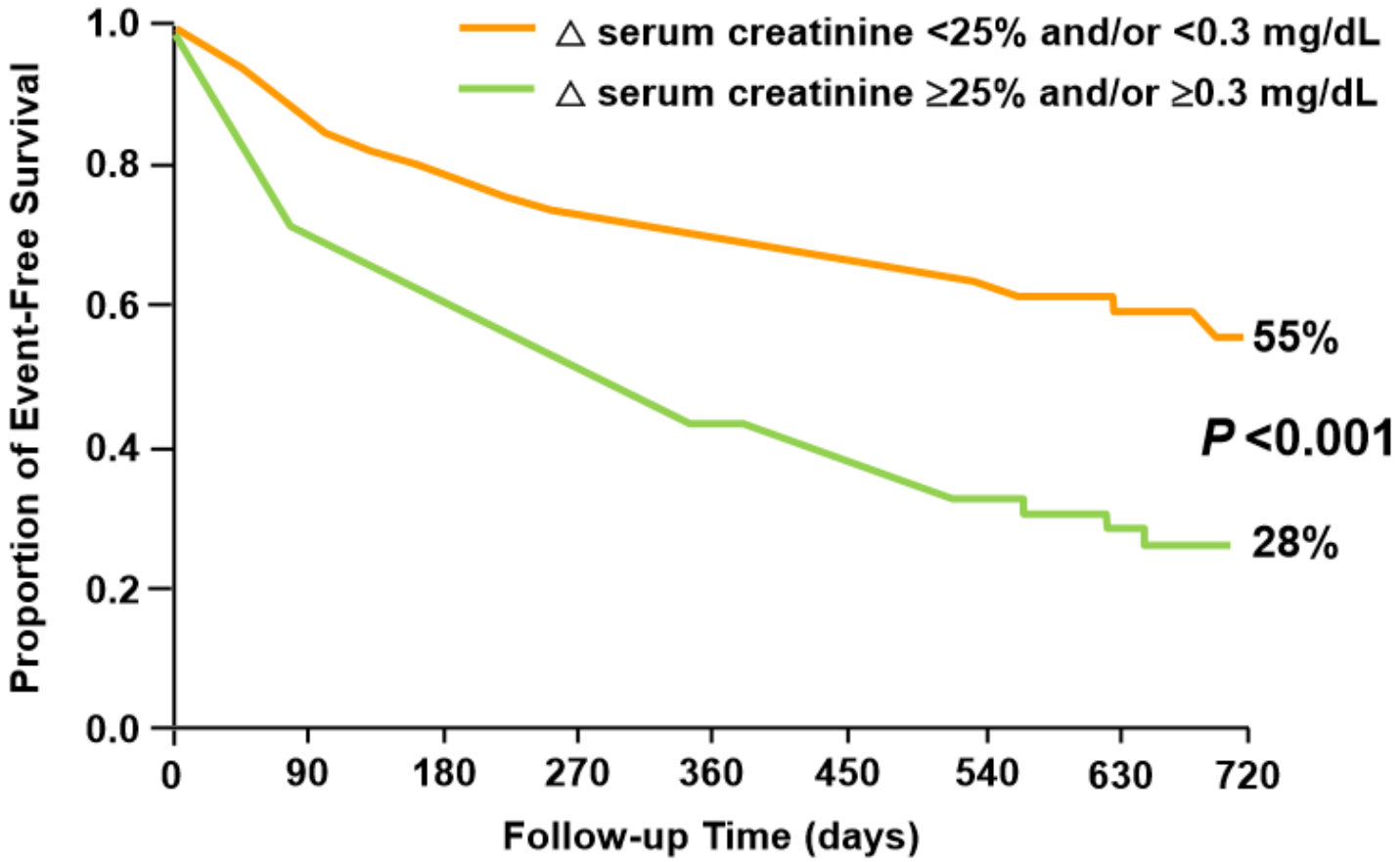
- **Conclusion**

  Acute or chronic dysfunction of heart or kidney may cause acute or chronic dysfunction of other organ. Based on the rapidity of onset and the primary organ which triggers the dysfunction, CRS can be classified into 5 types. Various biomarkers are available which can be used in conjunction with clinical evaluation to classify CRS.

Worsening renal function (WRF) contributes to increased mortality in acute heart failure



Metra M, et al. Eur J Heart Fail. 2008;10:188-195

ACC/AHA guideline summary: Management of patients with current or prior symptoms of heart failure (HF) and a reduced left ventricular ejection fraction (LVEF) (HF stage C)

Diuretics and salt restriction for fluid retention.

Data from Hunt, SA, Abraham, WT, Chin, MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119:e391.

Diuretics

Cornerstone in ttt as relieve congestion

Worsening renal function.

Activation of RAAS

No effect heart failure progression, mortality

Classes loop D, aldosterone Antagonist

Dose : minmium dose to relieve cong

Resistance or refractoriness : IV infusion, thaizide D

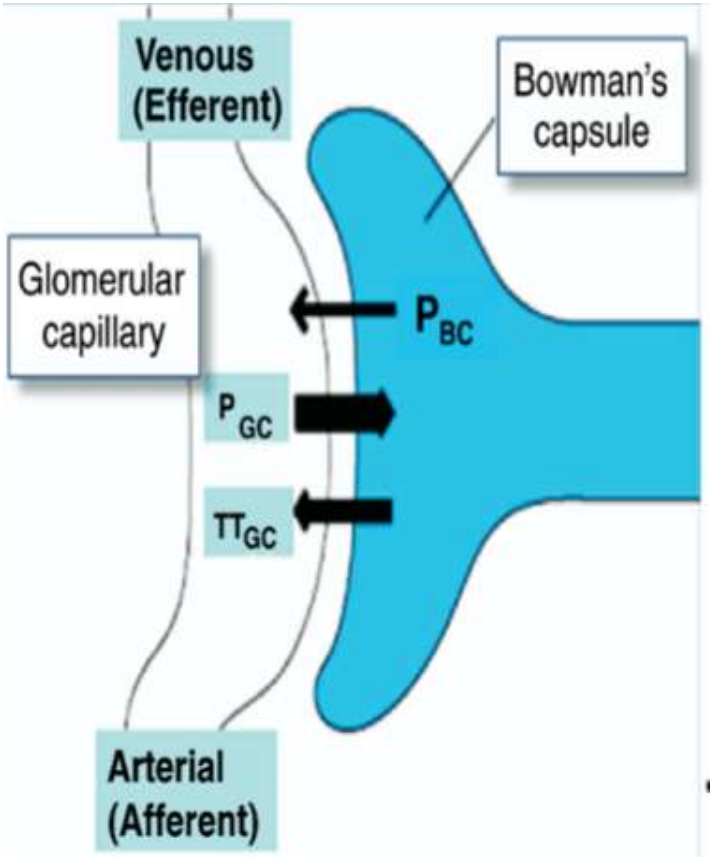
High doses of diuretics, which are a marker rather than a mechanism for poor outcomes.

Volz and Felker . **How to use diuretics in heart failure.** Curr Treat Options Cardiovasc Med. 2009 Dec;11(6):426-32.

Renal Replacement Therapy

1. Peritoneal dialysis (PD)
2. Intermittent Hemodialysis (IHD)
3. Slow Low-Efficiency Daily Dialysis (SLED)
4. Continuous Renal Replacement Therapy (CRRT)
   - Slow Continuous Ultrafiltration (SCUF)
   - Continuous Venovenous Hemofiltration (CVVH)
   - Continuous Venovenous Hemodialysis (CVVHD)
   - Continuous Venovenous Diafiltration (CVVHDF)

Impact of Venous Congestion on Glomerular Net Filtration Pressure



Forces	Normal: Afferent end of glomerular capillary (mmHg)	Normal: Efferent end of glomerular capillary (mmHg)	↑ RA pressure: Afferent end of glomerular capillary (mmHg)	↑ RA pressure: Efferent end of glomerular capillary (mmHg)
1. Favoring Filtration				
Glomerular-capillary hydrostatic pressure, P_{GC}	60	58	55	63
2. Opposing Filtration				
a. Hydrostatic pressure in Bowman's capsule, P_{BC}	15	15	15	15
b. Oncotic pressure in glomerular capillaries, π_{GC}	21	33	21	33
Net filtration pressure (1-2)	24	10	19	15
Filtration pressure:	*14 mmHg*		*4 mmHg*	

Jessup M, et al. J Am Coll Cardiol 2009; 53:597-9

Diuretics

- Mainstay of pharmacologic therapy
- No clear evidence of improved long-term mortality
- Rapidly efficacious in volume reduction
- Increase activation of RAAS & SNS
- Compromise renal perfusion, renal under filling

Diuretics in CRS

The well documented adverse effects of diuretics are:

- Hypotension
- Hypokalaemia and Hypomagnesaemia causing arrhythmias
- Loop diuretics block Na reabsorption by Macula Densa directly leading to Renin stimulation even in the absence of volume depletion [24]
- Volume depletion leading to further stimulation of RAAS/ SNS [25]
- Worsening Renal Function (WRF).